American Journal of Obstetrics and Gynecology

VOL. 28 ST. LOUIS, SEPTEMBER, 1934 No. 3

Original Communications

STUDIES RELATING TO THE TIME OF HUMAN OVULATION*

RAPHAEL KURZROK, PH.D., M.D., IRENE J. KIRKMAN, M.A., AND MARGARET CREELMAN, A.B., NEW YORK, N. Y.

(From the Departments of Obstetrics and Gynecology, and Biochemistry, and the Sloane Hospital for Women, the College of Physicians and Surgeons, Columbia University)

THE determination of ovulation and its exact time in the menstrual cycle are important from many viewpoints. Many cases of sterility are probably due to a failure of ovulation. Sociologically the determination of an exact safe period (on either side of ovulation) would solve the contraceptive problem for many, and thus remove from the technic of contraception many of its objectionable features.

The time of ovulation in the human being has been studied by six different methods, namely:

a. The macroscopic observation of the ovary in situ.

b. The microscopic examination of removed ovaries and uterine curettings.

c. The determination of the age of early embryos, taken together with the probable time of conception.

d. The maximum probability for ovulation.

e. The recovery of human ova from the uterine tubes.

f. The reversal in the reaction of the uterine muscle to pituitrin.

Based on the macroscopic examination of the ovaries Fraenkel and his school (Aneel and Villemin, 1907; Tschirdewahn, 1921; Derek, 1923) place the limits of ovulation between the tenth and twenty-sixth days of the cycle, with a maximum probability at about the eighteenth day.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

*Read before the meeting of the New York Obstetrical Society, January 9, 1934.

Robert Meyer, employing the histologic technic, concluded that the limits of ovulation were from the eighth to the fourteenth day of the cycle (Meyer and Ruge,[11] 1913). Using the same technic, Marcotty (1914) placed the most probable time of ovulation on the fifteenth day, and Schroeder (1918) from the fourteenth to the sixteenth day.

The third method of approach to this problem was the estimation of the age of early embryos, when considered together with the history and probable date of conception. Using such evidence Triepel (1914, 1915) placed the greatest frequency of ovulation at the eighteenth to the nineteenth day. Volkmann (1926) based his figures on the examination of eighteen early embryos and favored an earlier ovulation time. On the basis of similar studies Grosser placed ovulation between the second and twenty-fourth days after the onset of the menses. He thought that the early ovulation may have been induced by coitus, drugs, violent exercise, etc., as suggested by Chazan (1911).

The fourth method was by means of a study of the most probable time of conception (Siegel, 1917; Jaeger, 1917; Zangemeister, 1917). This presupposes that coitus, ovulation, and conception occur within an interval of hours, and that the ovum and sperm remain fertilizable not more than thirty-six hours (Hartman, 1932, review and literature). This method places the ovulation time between the eighth and tenth days. Ogino (1932) holds the favorable period of conception to be between the tenth and the seventeenth day.

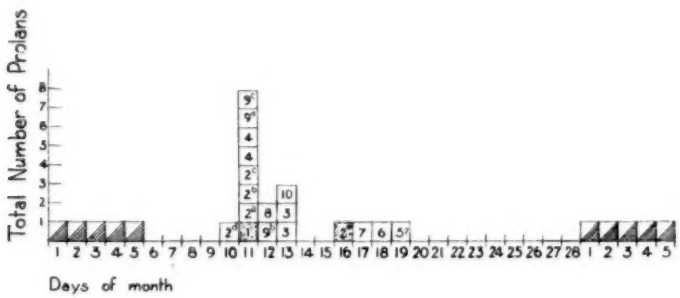


Fig. 1.—Prolan A excretion by days plotted on a twenty-eight-day cycle. Each square represents a prolan A excretion, the number within the square is the number of the case.

Dotted squares denote an ovulation followed by a pregnancy. The letters *a*, *b*, *c*, represent successive months.

(The form of the figure is suggested by Hartman's work on ovulation in the monkey.)

It has now been definitely demonstrated by the recovery of ova from the uterine tubes that in regular cycles of average length ovulation usually occurs during the intermenstruum. The estimated ovulation time for five human ova recovered from uterine tubes when possible stimuli of mating were excluded, was between the twelfth and fourteenth days following the first appearance of the menses (Allen, Pratt, Newell, and Bland, 1930). The probable time of ovulation of another human tubal ovum recovered by Lewis (1931) was placed on the eighteenth day following the onset of menstruation, after a previous cycle of thirty-five days' duration (E. Allen, 1932).

Another recent approach to this problem was suggested by Knaus. He observed that in the rabbit prior to ovulation, the uterus reacts to pituitrin by a contraction. Twenty-four hours after ovulation the uterus no longer reacts to pituitrin, and this reversal Knaus attributes to the corpus luteum. Knowing the date of reversal he places ovulation one day back (in the rabbit). Knaus

found the same reversal in the human being and placed ovulation from two days back, i.e., between the fourteenth and sixteenth days (of a twenty-eight-day cycle), with a possible physiologic shift of two days to either side. Wittenback (1930), on the basis of experiments in vivo, agrees with Knaus, but adds that ovulation may occur on the ninth day of a twenty-eight-day cycle. Knaus' method is not a test for ovulation but is really a test for corpus luteum hormone, because a corpus luteum may form without ovulation (corpus luteum atreticum). Hermstein (1931) agrees with Knaus' findings.

Two clinical signs of ovulation in the human being have been recognized by gynecologists, namely, the intermenstrual pain or "Mittelschmerz" and intermenstrual spotting. The former is probably due to the greatest distention of the follicle just preceding rupture. It is not common. It may be perfectly regular, occurring on one side one month, and on the opposite side the next. Or only one side may be involved, distention of the ovary on the opposite side causing no pain. Some

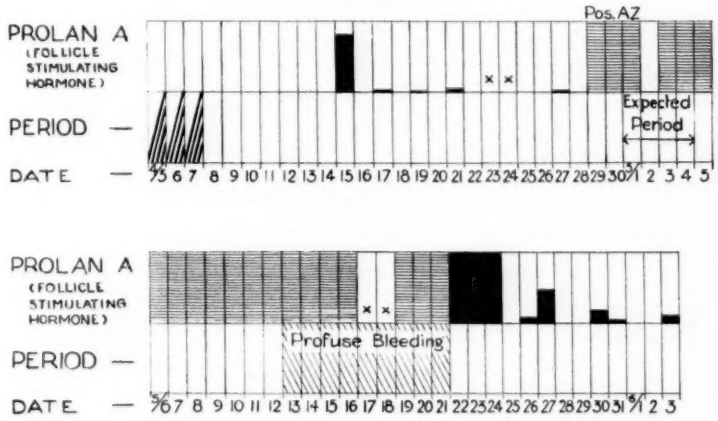


Fig. 2.—Case 1. Pregnancy.
Solid black denotes a positive prolan A reaction. The height of the column denotes the intensity of the reaction.
Cross ruling denotes a positive Aschheim-Zondek test.
X Denotes no specimen, or animals dead before completing the injections.

abnormality in innervation of the ovary is probably responsible for the phenomenon's reaching consciousness.

Intermenstrual spotting occurs quite infrequently. It may last from one hour to forty-eight hours, and the bleeding may be very slight or moderate. It has also been observed in the monkey (Hartman). Schroeder (1924) studied 20 cases, and curetted 5 during this period of abnormal bleeding. He found an endometrium that was in the process of changing from a proliferative to a premenstrual type, hence corresponding to the period of ovulation.

As a third indication of the time of ovulation we wish to add the sudden appearance of the follicle stimulating hormone (prolan A) in the urine of normal nonpregnant women.

METHOD

Morning specimens of urine were collected daily in each case. The number of such specimens varied with each patient, so that in some the daily excretion of hormone was studied for about two weeks, while in one case daily specimens

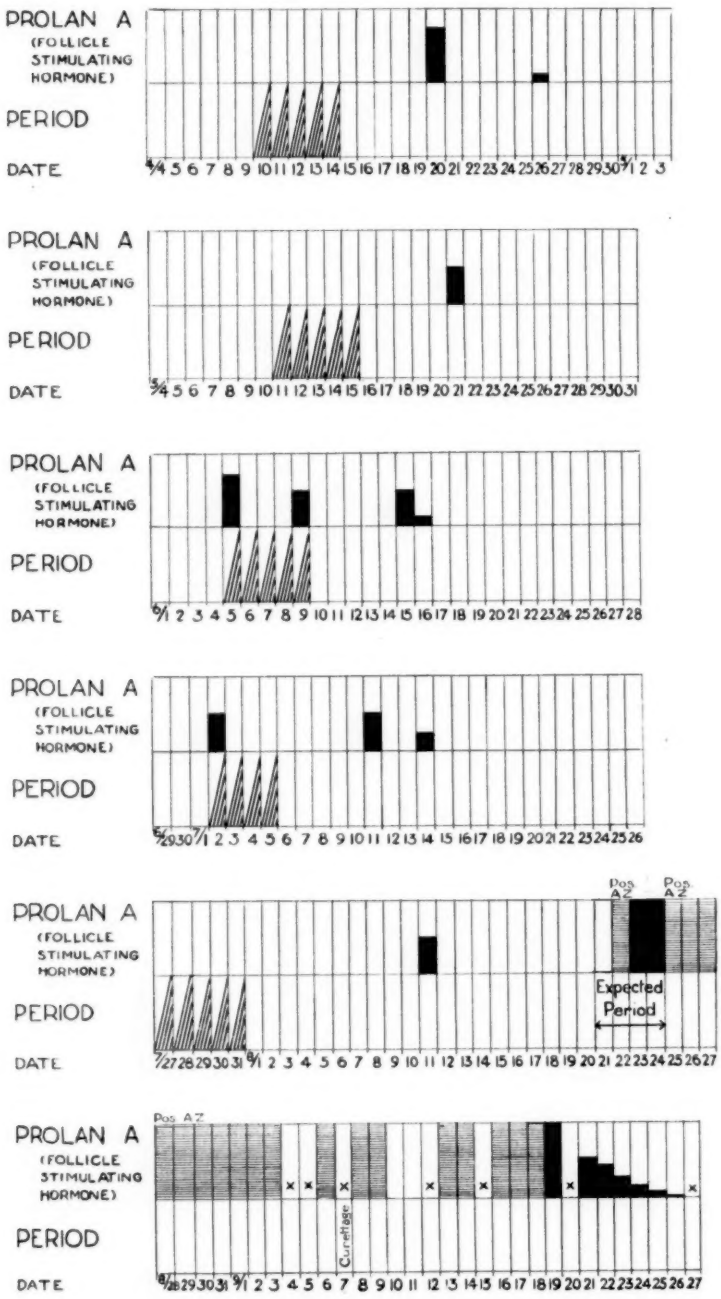


Fig. 3.—Case 2. Pregnancy.

were collected for more than seven months. The technic used for the determination of the follicle stimulating hormone (prolan A) was the one described by Zondek (1931).

CASE HISTORIES

CASE 1.—Patient aged twenty-six, nullipara, menses began at fourteen, twenty-six- to twenty-eight-day type, lasting four days, moderate in amount, last menstrual period from April 5 to April 7, 1933. Morning hormone determinations were carried out in this patient because she served as a control in a migraine investigation. It had been accepted, based on the work of Zondek, that normally menstruating women do not excrete the follicle stimulating hormone in the urine in quantities sufficient to detect it by Zondek's method (Zondek, 1931). On April 15, the eleventh day after the onset of the period, the urine showed the presence of follicle stimulating hormone. Fourteen days later, that is, on April 29, a positive Aschheim-Zondek test was obtained with this method. The expected period in May did not arrive. On May 13 the patient began to bleed profusely, passing large clots. This persisted through May 21. The bleeding was preceded by definite symptoms of pregnancy. The positive Aschheim-

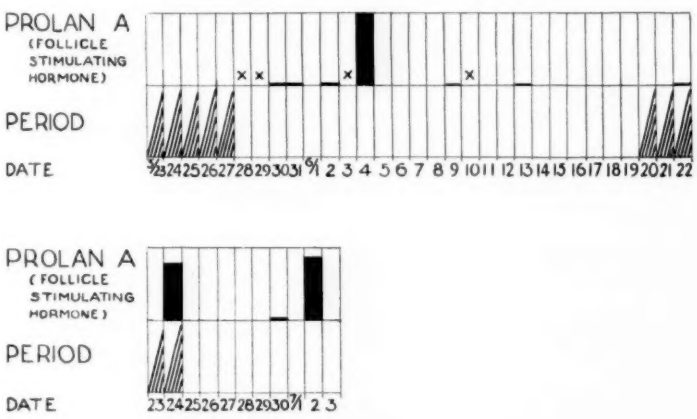

PROLAN A
(FOLLICLE STIMULATING HORMONE)
PERIOD
DATE
23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
PROLAN A
(FOLLICLE STIMULATING HORMONE)
PERIOD
DATE
23 24 25 26 27 28 29 30 1 2 3

Fig. 4.—Case 3. Normal control.

Zondek test persisted from April 29 to May 21 inclusive. (Additional tests by the routine Aschheim-Zondek method and by the Friedman method were all positive.) On May 22 the follicle stimulating hormone appeared in the urine and this persisted in gradually diminishing amounts up to June 3.

CASE 2.—This patient had been followed up for more than six months. A positive prolan A appeared after each menstrual period, in April, eleven days after the onset of the menses, in May eleven days, in June eleven days, in July ten, in August sixteen days. On August 22 a positive Aschheim-Zondek test appeared, a day after the expected period. A curettage was performed on September 7 and an early pregnancy was found. The positive Aschheim-Zondek test persisted through September 18 and a positive prolan A appeared on the following day. The latter reaction became gradually weaker and disappeared completely on September 29. It is of further interest to note that a positive prolan A appeared at the onset and at the end of the June period and again at the onset of the July period.

CASE 3.—A nullipara, aged twenty-five years, married, acted as a control. Menses began at fourteen years, regular, every twenty-six or twenty-eight days, five days in duration, moderate in amount and without pain. There was a posi-

tive prolan A thirteen days after the onset of the May period, and thirteen days after the June period. In addition a positive reaction appeared also on the last day of the June period.

CASE 4.—This patient, aged thirty, married, para ii, from twenty-three- to twenty-six-day cycle, acted as a control. A moderately strong reaction appeared on the eighth day of the June period and a strong reaction on the eleventh day. In July prolan A appeared eleven days after the onset of the flow, and there was also a mild reaction at the beginning and at the end of the period.

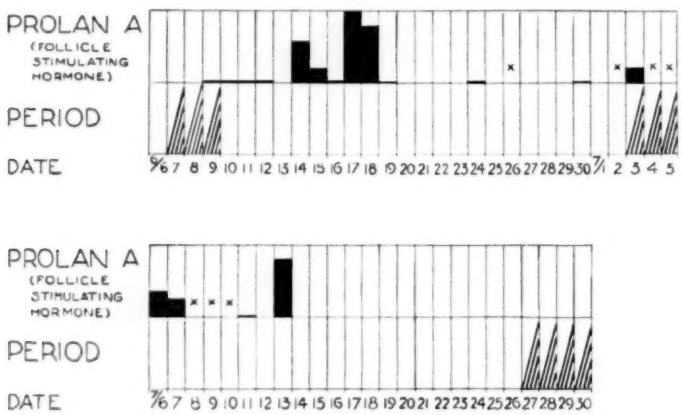


Fig. 5.—Case 4. Normal control.

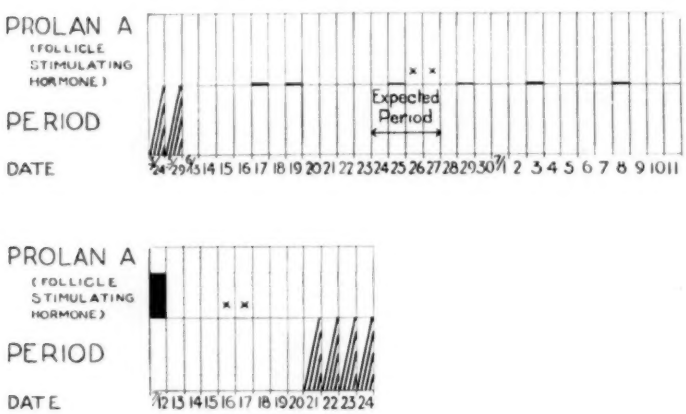


Fig. 6.—Case 5. Normal control. Ovulation without preceding menstruation.

CASE 5.—Patient aged twenty-four, married, nullipara, from thirty to thirty-one-day cycle occasionally a few days late, acted as a control. Prolan determinations were begun nineteen days after the onset of the May period. She skipped her June period, which was expected on the twenty-fourth, but was definitely not pregnant. There were no menstrual molimina. A positive prolan A reaction appeared on July 12, i.e., nineteen days after the expected onset of the period skipped.

CASE 6.—Patient aged twenty-eight, married, nullipara, from twenty-five- to twenty-seven-day cycle. Determinations were begun seven days after the onset of a five-day period (June). A positive prolan A did not follow the June period. The

July period was perfectly normal and a positive reaction was demonstrated eighteen days after the onset of the period. A moderate reaction appeared at the end of the period.

CASE 7.—Patient aged six and a half years. Precocious sexual maturity. Menstruation began at two and a half years, from twenty-six- to twenty-eight-day cycle, four to five days' duration, moderate in amount and without pain. There was an abundant pubic hair growth as well as considerable development of the breasts. No pelvic pathology could be made out, except the expected enlargement of the uterus as compared with one usually found in a girl of seven. Diagnosis:

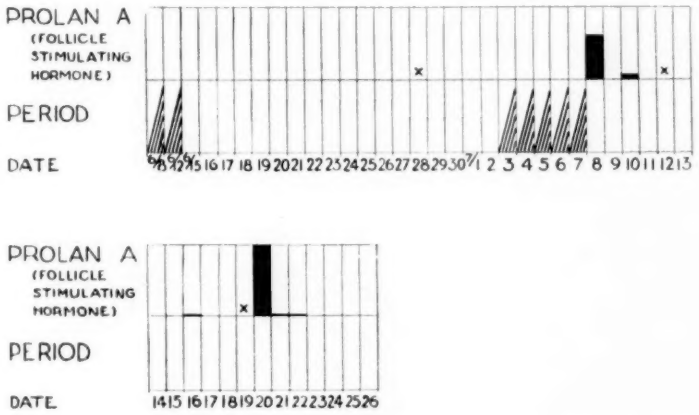


Fig. 7.—Case 6. Normal control. Probably menstruation without ovulation.

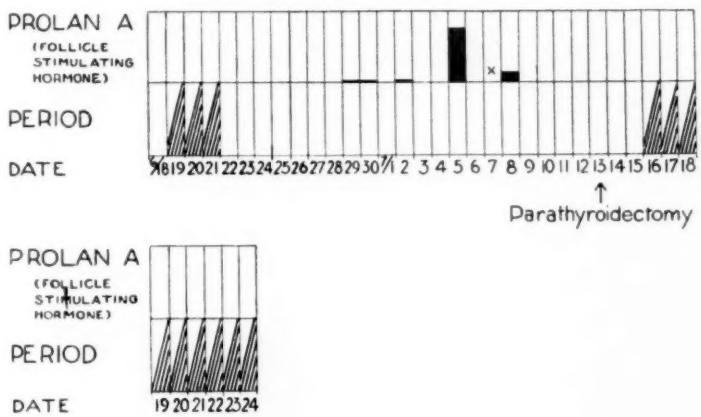


Fig. 8.—Case 7. Ovulation in a case of precocious sexual maturity, age six and a half years.

osteitis fibrosis cystica. Positive prolan A appeared seventeen days after the onset of the June period.

CASE 8.—Patient aged sixteen, admitted to the hospital for "Mittelschmerz." Menses twenty-eight-day type, lasting seven to eight days, accompanied by slight lower abdominal pain, usually in the left lower quadrant but occasionally in the right. The left-sided pain was more severe. Rectal examination revealed a uterus normal in size, shape, and consistency. Adnexa palpable but not pathologic. During the period of observation the pain appeared on the morning of August 21, i.e.,

twelve days after the onset of the period. The pain was sharp, localized to the left lower quadrant, lasted five hours, developed slowly but disappeared rapidly. A positive prolan A reaction was found ten days after the onset of the period, or one day before the "Mittelschmerz."

CASE 9.—Patient aged twenty-nine, para ii, menses twenty-eight-day type, lasting five days, moderate in amount. Patient had migraine attacks and was studied because of these attacks. A positive prolan A was obtained twelve days after the January period and eleven days after the February period. A positive prolan A

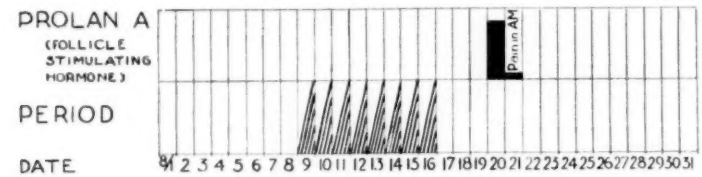
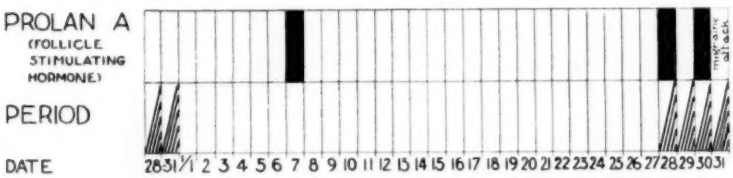
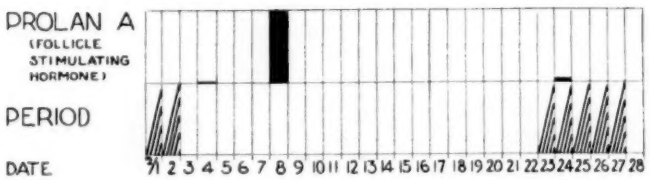


Fig. 9.—Case 8. "Mittelschmerz."





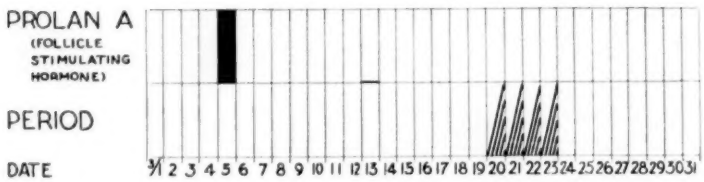


Fig. 10.—Case 9. Migraine attack during January period.

also was demonstrated the first day of the January period and also on the third day of the period. This latter occurred one day preceding a severe attack of migraine.

CASE 10.—Patient aged twenty-eight, single, menses twenty-eight-day type, lasting four days. Usually at about halfway between two periods the patient spotted, this lasting anywhere from six to forty-eight hours. Occasionally there was an intermenstrual period without spotting. Following the August period there was no spotting and no prolan A appeared in the morning urine. Following the September period (first to fifth) prolan appeared on the thirteenth day and spotting occurred on the same and the following days. There was no spotting after the October period and no prolan.

DISCUSSION

The appearance of a positive prolan A reaction in the urine in these patients at about the middle of the intermenstrual intervals immediately suggests that this excretion is closely related to the phenomenon of ovulation. It has now been definitely demonstrated that the stimulus for ovulation proceeds from the anterior pituitary gland, the site of elaboration of prolan A. Its sudden appearance in the urine for a short period denotes a sudden activity of this gland. We consider this to be the *stimulus to ovulation*, but whether ovulation will actually take place depends upon whether the ovary is normal or pathologic. In two cases we actually know that ovulation did take place (Cases 1 and 2) for pregnancy occurred in both. Whether ovulation occurs also in the absence of this sudden prolan A excretion, will be decided by a further study of many cases, especially those wherein pregnancy occurs during the period of observation, or in those where tubal ova are found.

The time relationship between the sudden excretion of prolan A and actual ovulation is of great interest. We assume that ovulation follows the prolan A excretion in twenty-four hours. The evidence is indirect. In the rabbit ovulation follows the intravenous injections of prolan in about twenty-four hours. In the case of the patient with "Mittelschmerz" (Case 8) the pain followed the excretion of prolan by twenty-four hours. Clinically we believe that the pain at "Mittelschmerz" is due to the greatest distention of the follicle, i.e., just prior to rupture. Additional evidence is furnished by Cases 1 and 2. The intervals between the appearance of a positive prolan A and a positive Aschheim-Zondek test were thirteen and ten days, respectively. The appearance of a positive Aschheim-Zondek test in all likelihood denotes nidation of the ovum (a point that will be considered later). These intervals cover the period of fertilization, migration of the fertilized ovum through the tube and uterus, and nidation. The time occupied by these processes is considered by embryologists to be ten days. This, therefore, would bring the appearance of prolan A and ovulation very close together. (Absolute proof for time relationship will be at hand only when a recently discharged ovum is found in the tube of a patient in whom a positive prolan A had previously been demonstrated.)

Interesting relationships between ovulation and menstruation are brought out by Cases 5 and 6. The patient in Case 5 may have ovulated early in June but our tests did not begin until June 13. The expected June period did not appear. This control was occasionally several days overdue, but this time she was overdue four weeks. A positive prolan A appeared nineteen days after the expected onset of the June period (June 24). This would tend to show that ovulation can occur independently of menstruation. (The date of the prolan excretion is here given on the nineteenth day from the expected onset of the

period, computed on the supposition that she should have menstruated on the twenty-fourth day of June. The expected period could have been a few days later and this would have shifted the date of the prolan excretion toward the middle of the cycle.)

Case 6 illustrates another relationship between ovulation and menstruation. There was no excretion of prolan A between the June and July periods (the cycle under consideration). No prolan determinations were made on the sixth, seventh, and twenty-first day of the cycle. The probabilities are against ovulation occurring on these days, so that we may have here a menstrual cycle during which no ovulation has occurred. This would also tend to confirm the idea that ovulation and menstruation are independent phenomena and that one may occur without the other.

Case 7 demonstrates ovulation in a patient six and a half years of age, hence potentially capable of pregnancy.

Schroeder's work on the intimate relationship between intermenstrual spotting and ovulation is supported by Case 10. Here the positive prolan coincided with the spotting. In two other cycles wherein the spotting did not appear no prolan appeared in the urine. This gives support to the idea that the spotting is pituitary in origin, and this latter idea, carried a step further, furnishes some insight into the etiology of menstrual bleeding per se. Cases 2, 4, and 9 showed a positive prolan on the first day of the menstrual period. That this does not represent ovulation is agreed upon by all investigators, that is, ovulation and menstruation are not coincident. It suggests that menstrual bleeding is induced by a stimulus from the anterior pituitary gland, and not by a withdrawal of corpus luteum hormone. Or, we may formulate the notion that the lessening or loss of corpus luteum activity produces a liberation of prolan A and menstrual bleeding occurs. The experiments of Hartman, Firor, and Geiling (1930) suggested that the anterior pituitary is essential for the process of menstruation in monkeys. That the excretion of prolan A on the first day of the menstrual period is not an essential phenomenon is shown by its absence during the menstrual periods that were followed by pregnancy (Cases 1 and 2). The appearance of prolan A in the urine at the end of menstruation is not easy to explain. It may suggest that the stopping of the hemorrhage requires further pituitary activity. In Case 9 the excretion occurred a day previous to a severe attack of migraine, a phenomenon already described by Riley, Brickner, and Kurzrok (1933).

Fig. 1 represents the dates of the prolan A excretion plotted against a twenty-eight-day menstrual cycle. The grouping would remain the same for ovulation except shifted one day to the right. It will be noted that the greatest number of ovulations occurred on the twelfth day, and that the greatest frequency of ovulation was between the eleventh and four-

tenth days. The earliest day of ovulation was on the eleventh day and the latest on the nineteenth or twentieth day (Case 5). The position of Case 5 in the chart is possibly incorrect for we do not know the exact onset of the previous menstrual cycle. Case 2 gives some interesting data with regard to the so-called safe period. Ovulation occurred once on the eleventh day and three times on the twelfth. One would have been tempted to tell this patient that her safe period was after the fourteenth day of her cycle. But the very next month ovulation occurred on the seventeenth day, and conception then took place. Whether such wide variations occur in other women can be shown only by an extensive series of cases.

Cases 1 and 2 yield some interesting information with regard to the Aschheim-Zondek test for pregnancy. The period between ovulation and the appearance of a positive Aschheim-Zondek test covers fertilization, migration of the fertilized ovum through the tube and uterus, and nidation of the ovum. It is now held that the first appearance of a positive Aschheim-Zondek test denotes nidation of the ovum and an interchange of products between the chorionic epithelium and the maternal blood stream. Unfortunately, we do not know the exact dates of coitus in either case, but we may assume that fertilization did not take place later than forty-eight hours after ovulation. This is on the assumption that spermatozoa are not capable of fertilizing if they remain in the female genital tract for more than forty-eight hours. Migration of the fertilized ovum through the uterus and tubes takes about ten days, of which two-thirds is passed in the tube and one-third in the uterus, this according to embryologic evidence gathered by Grosser. Nidation, according to this same writer, takes two days. Cases 1 and 2 suggest the following possible sequence of events:

CASE	PROLAN A EXCRETION	OVULATION	PROBABLE DATE OF FERTILIZATION	MIGRATION OF OVUM	NIDATION	POS. A-Z	
						DAY OF CYCLE	AFTER OVULATION
1	11th day	12th day	13th day	10 days	23-24th day	25th	13th
2	16th day	17th day	18th day	7 days	25-26th day	27th	10th

Another problem illuminated by these two cases is the time of the first appearance of a positive Aschheim-Zondek test. Aschheim (1933) states that according to his observation the earliest positive test occurred thirty-one days after the last menstrual period. He cited one case where the test was positive three days after the expected onset of the skipped period, and another which occurred sixteen days after a single coitus. Goecke (1930) mentions a positive case twenty-one days after the last period (but does not mention the duration of the period) and seventeen days after coitus. Bruhl (1932) reports a positive case three

days after the failure of the period to appear, and also another where the test became positive fourteen days after a single coitus. In our series, Case 1 became positive on the twenty-fifth day of the cycle or two days before the expected onset of the skipped period. Case 2 was positive on the twenty-seventh day of the cycle or one day after the expected onset of the skipped period.

The question of the multiplicity of the gonad stimulating hormones of the anterior pituitary is still unsettled. Are the follicle stimulating hormone (prolan A) and the luteinizing hormone (prolan B) identical or two different substances? Cases 1 and 2 are suggestive of two hormones. When the pregnancies were terminated, a positive Aschheim-Zondek test suddenly became a positive prolan A reaction, which gradually subsided in about ten days. Such a sudden change in the reaction of the ovaries can best be explained by the idea that the positive Aschheim-Zondek test is due to prolan A (follicle stimulating hormone) plus prolan B (luteinizing hormone) while the appearance of follicles is due to prolan A alone.

CONCLUSIONS

1. Ten young women were studied for their daily prolan A (follicle stimulating hormone) excretion over extended periods.

2. Sudden excretion of this hormone occurred at about the middle of the menstrual cycle, and had a definite tendency to recur at about the same time in the following cycle.

3. This sudden secretion of prolan A from the anterior pituitary is considered to be the stimulus to the ovaries to induce ovulation.

4. Evidence is given in support of the view that ovulation follows the prolan A excretion in about twenty-four hours. It is believed that ovulation cannot occur without this stimulus of prolan A. The presence of this substance is not, however, prima facie evidence that ovulation has occurred.

5. The time of ovulation as suggested by this method is in complete agreement with the results of all other methods used in the study of this problem.

6. The greatest incidence of prolan A excretion was between the tenth and thirteenth days, hence, the greatest incidence of ovulation was between the eleventh and fourteenth days.

7. One case (Case 6) suggests the possibility of menstruation without ovulation, and another (Case 5) of ovulation without previous menstruation.

8. Two of the patients (Cases 1 and 2) thus studied became pregnant while under observation; the course of events was noted in both, from menstruation through the termination of pregnancy.

9. Suggestive time relationships between menstruation, ovulation, fertilization, migration of the fertilized ovum, and nidation are considered.

10. Cases 1 and 2 show the very early appearance of a positive Aschheim-Zondek test, namely, on the twenty-fifth and twenty-seventh days from the onset of the last menstrual period, or two days before and one day after the expected onset of the skipped period.

11. The sudden conversion from a positive Aschheim-Zondek test to a positive prolan A reaction at the end of pregnancy is suggestive of a multiplicity of the gonadotropic hormones from the anterior pituitary gland.

The authors are indebted to Professors Philip E. Smith and Earl T. Engle for their kind criticism of this work. Also to Professor Henry A. Riley and Dr. Richard Brickner for the use of Case 1, and to Professor Irving Pardee for the use of Case 2. We are also indebted to Professor Benjamin P. Watson for his kind cooperation and encouragement.

REFERENCES

Allen, Edgar, Pratt, J. P., Newell, Q. U., and Bland, L. J.: Contrib. Embryol. No. 127, Carnegie Inst. Wash. **22:** 47, 1930. *Allen, E.:* Sex and Internal Secretion, Baltimore, 1932. *Ancel, P., and Villemin, F.:* Compt. rend. des seances de la soc. de biol., Paris, 1907. *Aschheim, S.:* Die Schwangerschaftsdiagnose aus dem Harne, Berlin, 1933. *Bruehl, R.:* Ztschr. f. Geburtsh. u Gynäk. **101:** 403, 1932. *Chazan, S.:* Die Beziehung der Konzeption zur Menstruation, Zentralbl. f. Gynäk. **35:** 648, 1911. *Derek, St.:* Das zeitliche Verhaltnis von Ovulation und Menstruation, Diss. Breslau, 1923. *Fränkel, L.:* Physiologie der Weiblichen Genitalorgane. Halban-Seitz. **1:** 517, 1924. *Goecke, H.:* Arch. f. Gynäk. **144:** 487, 1930. *Grosser, Otto:* Zentralbl. f. Gynäk. **56:** 706, 1932. *Hartman, C. G., Firor, W. M., and Geilung, E. M. K.:* Am. J. Physiol. **95:** 662, 1930. *Hartman, Carl G.:* In E. Allen, Sex and Internal Secretions, Baltimore, Williams and Wilkins, Chap. 14, 1932. *Hermstein, A.:* Zentralbl. f. Gynäk. **55:** 2887, 1931. *Jaeger, F.:* Zentralbl. f. Gynäk. **41:** 857, 1927. *Knaus, H.:* Zentralbl. f. Gynäk. **53:** 2193, 1929. *Lewis, W. H.:* Bull. Johns Hopkins Hosp. **48:** 368, 1931. *Marcotty, A.:* Arch. f. Gynäk. **103:** 63, 1914. *Meyer, R., and Ruge, C. H:* Zentralbl. f. Gynäk. **37:** 50, 1913. *Ogino, L.:* Zentralbl. f. Gynäk. **56:** 721, 1932. *Riley, H. A., Brickner, R. M., and Kurzrok, R.:* Bull. Neur. Inst. of N. Y. **3:** 53, 1933. *Schroeder, R.:* Arch. f. Gynäk. **101:** 1, 1914. *Idem:* Zentralbl. f. Gynäk. **42:** 633, 1918. *Idem:* Die Pathologie der Menstruation. In Halban-Seitz. Biologie und Pathologie des Weibes. Berlin **3:** 962, 1924. *Siegel, W. P.:* Gewollte und ungewollte Schwankungen der Weiblichen Fruchtbarkeit, Bedeutung des Cohabitationstermins für die Häufigkeit der Knabengeburten, Berlin, 1917. *Idem:* Zentralbl. f. Gynäk. **45:** 984, 1921. *Triepel, H.:* Anat. Anz. **46:** 385, 1914. *Idem:* Anat. Anz. **48:** 133, 1915. *Tschirdewahn, F.:* Ztschr. f. Geburtsh. u. Gynäk. **83:** 80, 1921. *Volkmann, K.:* Monatschr. f. Geburtsh. u. Gynäk. **73:** 58, 1926. *Wittenbeck, F.:* Arch. f. Gynäk. **142:** 446, 1930. *Zangemeister, W.:* Arch. f. Gynäk. **107:** 405, 1917. *Zondek, B.:* Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, 1931, p. 251.

DISCUSSION

DR. EARL T. ENGLE.—This substance which is obtained from the urine of normal women is, as Dr. Kurzrok emphasized, very similar to the factor in the anterior pituitary gland. It is not to be confused with a similar factor in the urine of pregnant women, nor with that in cases of chorionepithelioma. It is very similar, probably is identical, with the hormone in the urine in menopause cases.

Dr. Kurzrok has shown the appearance of this active principle in a sequential relationship to the suspected time of ovulation. Many more cases are needed to prove the point, but the tentative conclusion of a causal relation between the ap-

pearance of this material in the urine and the suspected stimulus to ovulation from the anterior pituitary appears to be justified.

Of the new developments that have come from the laboratory not the least important has been the refinement of technic in biologic, physical, and chemical tests to aid the physician.

I am rather hopeful that the work which Dr. Kurzrok has done, and the study that he has given this small group of cases, will result in another biologic test which will be of importance in the diagnosis of ovulatory activity.

DR. ROBERT L. DICKINSON.—In 1932, I read before the Society a brief summary of a short study of ovulation as the result of bimanual examinations at intervals of two or three days on five patients. These demonstrated the changes in the ovary, and coincident and marked alteration in the cycles of contraction of the uterus. In the pre- and postovulatory divisions of the menstrual cycle quiescence in contraction was found; mild contractions during menstruation, and very marked rhythms of relaxation and contraction at the time of the swelling and tenderness in the ovary. In well-marked examples the compressibility and elasticity of isthmus and corpus is then as striking as in early pregnancy, and the rhythm from one to eight minutes.

The preliminary report was not printed, but the material appears in part in my *Atlas of Human Sex Anatomy*, page 28 and Figs. 38 to 40, under date of observation of April to June, 1932.

DR. ROBERT T. FRANK.—I would like to ask Dr. Kurzrok how much urine he uses for a concentration test. What is the amount required?

DR. RAPHAEL KURZROK.—Sixty cubic centimeters.

DR. FRANK.—I feel rather sorry for the clinician who, not directly engaged in laboratory work, attempts to follow the intricacies of these subjects; although I have been, and still try to be both clinical and laboratory investigator I find it very hard myself.

You should realize that the tests we are speaking of here are based on the reaction of the ovary. What the speaker called prolan A simply means the reaction of the immature mouse ovary in the formation of numerous enlarged follicles. What he terms prolan B is the reaction we find as the result of pregnant urine, the typical Aschheim-Zondek test. The terminology I use is APR II for blood spots; that is, hemorrhage into luteinized follicles or APR III, the formation of corpora lutea. These reactions, as far as the clinical interpretation is concerned, are entirely distinct from the one representing a nonpregnant reaction—prolan A (APR I) follicle stimulation, which you find in some parts of the cycle, or which you find after the menopause, or which you may obtain from male urine; the punctate hemorrhages, which are small in the mouse and usually large in the rabbit, and the corpus luteum formation are evidence of pregnancy or its homologue, chorionepithelioma.

My own work has been mainly centered on the blood. Our schema based upon a large number of normal fertile, menstruating females, has shown that in the blood about the ninth day there is an easily determinable quantity of prolan A, if you so want to call it; that is, you get a follicle growth reaction in the ovary of the immature mouse; during the rest of the cycle only a minimum quantity is present in the circulation. The fact that the maximum in the blood appears on the ninth day, in the urine on the eleventh, would again show that it takes a day or two before it is excreted in the urine. In other words, in the blood and in the urine there is a time when there is more of this hormone or hormone-like substance circulating. This time in the blood is about the ninth day, using the first day of the

menstruation as the beginning point in the blood, and about eleven days, taking Dr. Kurzrok's figures, in the urine. What interpretation should be given this? I know of no more unsatisfactory animal to study than the human female; there are so many distracting factors. I would much prefer, if I could do so, to have the material which is at Dr. Engle's disposal—the controllable monkey. On the other hand, as clinicians we have to content ourselves with the human female in many instances. Now, what interpretation shall we give to the findings? I myself have ventured to say that this blood reaction on the ninth day presupposes the stimulation necessary for ovulation: that is as far as I am willing to go. Menstruation in itself means nothing because it has been definitely determined that all that is needed for menstrual bleeding is a uterus and the priming of the uterus with female sex hormone up to a certain point and then its abrupt withdrawal. That holds true of the primates of all classes, including the human female. That does not mean a perfect cycle. It means a menstrual bleeding resulting from this pharmaceutical treatment, if you wish to call it such, sometimes brought about by nature, but also artificially producible. That does not necessarily imply that a monkey or human female can conceive, because, in addition, a corpus luteum is necessary for the sensitization or preparation for nidation. It therefore is evident that we have numerous factors to consider. The corpus luteum, however, we cannot demonstrate by hormone titer, because we have no available tests. Therefore, the only deductions that I am willing to draw from both my blood investigations and the urine investigations of Dr. Kurzrok are that in those individuals in whom in the blood or in the urine, or preferably in both, you find the presence on the ninth and eleventh days of this kind of hormone the prepituitary, the adenohypophysis, is cyclically acting. Whether ovulation occurs depends on so many extraneous factors that I do not believe this can be considered as proved by these tests. Now, what Dr. Engle says about the presence of a prepituitary-like substance in the blood and urine of the menopausal female, whether the menopause is physiologic or artificial, is difficult to interpret. Whether it means there is any utilization or not I do not know. Of course, I feel at the moment absolutely ignorant in what fashion hormones are utilized at the site where they are active. So far as the intermenstrual bleeding is concerned, again many extraneous factors must be considered. The congestion which occurs during the late intermenstrual period and the many traumas to which the cervix is exposed make it extremely doubtful, in my opinion, whether this finding can be used as any criterion.

DR. RAPHAEL KURZROK.—There is very little that I can add. I told you that I did not bring absolute proof, but this is more than suggestive evidence of ovulation. One must admit that the two patients who became pregnant ovulated, and certainly ovulation must have occurred close to the day of prolan A excretion, if the other facts about the Aschheim-Zondek test are correct. If the follicle stimulating hormone is an anterior pituitary product, and if the anterior pituitary induces ovulation, I do not see how you can possibly escape the correlation between prolan A excretion and ovulation except by arguing that the two are not intimately bound up.

NONCONVULSIVE TYPES OF TOXEMIAS IN LATE PREGNANCY*

OTTO H. SCHWARZ, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital and Barnes Hospital)

SINCE 1922, the general advantages of the conservative treatment of eclampsia over active intervention, have been emphasized. The conservative treatment has been generally adopted. In certain localities, however, active intervention is still practiced successfully. However, as Stander has shown, when a large analysis of cases is made, from various parts of the world, the advantage of the conservative treatment is readily seen. Today, I think it can be safely said that, in general, some sort of conservative treatment is instituted primarily, followed by more radical measures, especially in those cases which do not respond satisfactorily to some form of conservative procedure.

In 1929, we reported our results at the St. Louis Maternity Hospital and City Hospital. The maternal mortality rate for 186 cases was approximately 7 per cent. It is, however, discouraging to mention that during the last four years, we have treated 31 patients in the St. Louis Maternity Hospital with 7 maternal deaths. During this time, as a result of much information that has been gathered concerning the toxemias, we have instituted procedures which we feel were far from empirical and, therefore, the most logical to use in active cases of eclampsia. In spite of this, and resorting to radical measures, after conservative treatment had been employed and had not given the desired results, these rather poor results were obtained. It might be interesting, however, to mention that in the case of the death of these patients, most of them were not seen in any prenatal clinic or at least had not reported for proper observation.

I am forced, from our recent experiences, to believe that the methods of conservative treatment have yet to be modified definitely and improved. From the above facts and also from the experience of a prenatal clinic, where patients are observed carefully, and the fulminating type of eclampsia seldom develops, it would seem that prophylaxis after all is the most important. If a late toxemia of pregnancy does develop under such care, if it is of the low reserve kidney type, preeclampsia or nephritic toxemia, seldom does it develop the convulsive

*Read at a meeting of the Chicago Gynecological Society January 19, 1934.

state. Therefore, I believe that the chief factor in lowering the maternal death rate in eclampsia does not so much lie in the improvement in treatment but rather in seeing that each and every expectant mother can avail herself of the proper prenatal care.

Perhaps just as important if not more so, are the cases of nonconvulsive late toxemia; not so much because they lead to maternal mortality, but rather because of handling them too conservatively and over a long period of time, certain damaging effects can develop which will leave these patients, so far as their kidney function is concerned, permanently and definitely impaired.

I thought it might be interesting, therefore, to go over our own cases of nonconvulsive toxemia during the past four years and state briefly how they were handled and what were the immediate results so far as mother and child are concerned. It had been my impression that the treatment of these cases had been rather fully discussed, but to my surprise during the last three or four years, I could find very little in the literature on the management of nonconvulsive types of toxemia.

Much work has been done by Stander and his associates to classify these late nonconvulsive toxemias and as this classification is quite satisfactory, it has been more or less universally accepted. The chief difference between Stander's and previous ones, is that he divides the milder hypertensions and albuminurias from the so-called preeclampsias. It might be well here to mention the features of Stander's so-called low reserve kidney.

1. An elevated blood pressure, which at the end of the puerperium has dropped to a normal level. In most instances this elevation is not very marked, rarely exceeding 150 systolic and 90 diastolic.

2. The amount of albumin in the urine is never very great, varying before delivery between a fraction of a gram and two grams per liter, although the lower figures are most usually observed. The albumin disappears during the puerperium, and the patient leaves the service either with no albumin at all, or with at most 0.1 gram per liter.

3. The outstanding characteristic is the fact that, in subsequent pregnancies, the patient's condition does not become aggravated and she is as well as, or better than, she was in the preceding pregnancy.

He also states that the prognosis of these cases is good, interruption of pregnancy is not indicated, rest in bed and low protein diet with restriction of salt is recommended. If improvement does not take place under such conditions, he feels that the case is probably one of nephritis complicating pregnancy. According to Stander, the main differential points in the preeclampsia from the low reserve kidney are chiefly in the finding of an increasing uric acid content and a lowered CO_2 combining power. The condition usually does not de-

velop until the last two months of pregnancy and the onset is abrupt. Within a short time the blood pressure rises to as high as 190 systolic. The eyegrounds show edema of the retina and retinal hemorrhage. In discussing the treatment of these cases, Stander states that these patients should be hospitalized and steps be taken to prevent the outbreak of eclampsia. The patient should be in bed and proper dietary measures instituted. He suggests that some conservative form of treatment, such as a modified Stroganoff treatment, be used. He points out that unfortunately, all preeclamptics do not respond to conservative methods of treatment, and it is necessary to deliver the patient to forestall the outbreak of eclampsia. He believes that the induction of labor in the multiparous patient from below is the procedure of choice. In the primiparous woman, the method of delivery offers more difficulty and unless favorable conditions for induction or delivery from below exist, cesarean section without a general anesthetic appears to be the procedure of choice.

Although there are some reports stressing more active interference in these cases, it is rather surprising that during the last four years, there is very little suggested as to the proper handling of these patients. Adair and Dieckmann reported their experiences and ideas concerning this group of toxemias at the last meeting of the American Gynecological Society (1933). I shall not mention any of the results of their study here, hoping that they will review their ideas on this subject in the discussion of my paper.

There are, however, several things that are not usually emphasized concerning the ultimate results of these cases, which have to do with the pathologic lesions developing from their occurrence. In the first place, it is well known that fetal mortality in cases that have carried a high blood pressure during pregnancy, is exceedingly high, especially where the hypertension has existed since the middle of pregnancy, as is often seen in the nephritic types of the toxemias where the chances of the fetus are frequently bad. These are the cases in which marked infarction of the placenta occurs, robbing the fetus of its blood supply. This infarction, we believe is due to the fact that marked arterial changes take place, chiefly due to the hypertension. The changes which take place are similar to those occurring in ordinary involution and I believe it might be of interest to review these processes as well as the pathology of the kidney in the late toxemias and to what developments they can lead. These kidney changes of eclampsia are present in a moderate degree in all cases of hypertension in late pregnancy and in the case of the nephritic toxemia, the picture is superimposed upon the already damaged kidney. The long continued hypertension in the kidney can cause permanent effects and, therefore, in an individual who carries a hypertension for any

length of time great risk will be run of having the kidneys permanently damaged as a result of a sclerosis of the arterial system of the kidney. One of the best studies of the late results of the nonconvulsive types of toxemias is a recent one by Peckham and Stout. I mention some of their chief conclusions:

Of a series of 545 consecutive deliveries of toxemic patients, excluding eclampsia and vomiting, 66.6 per cent have been reexamined four months to four years after delivery, and at that time 40 per cent of them have been found to have definite chronic nephritis.

The differential diagnosis between nephritic and nonnephritic toxemia frequently cannot be made during pregnancy or the puerperium, and even at six weeks after delivery, the diagnosis is sometimes incorrect.

Nephritis is seen more frequently in the older age groups and among multiparas. Two-thirds of the nonnephritic toxemias occur in women under twenty-five, and a similar proportion are primiparas.

The phenolsulphonephthalein and Mosenthal renal function tests give almost identical results in the two types of cases.

Only 7 per cent of nonnephritic patients show hypertension or albuminuria prior to the seventh month of pregnancy, while over half the nephritics were known to be abnormal at that time. However, almost a fifth of the women who ultimately were diagnosed as nephritic were known to be normal until after the seventh month. This would seem to indicate that chronic renal damage may be a result of the toxemic process.

In reporting our experience with the nonconvulsive types of toxemias, I have made no attempt in this brief report to classify them into various groups, but have grouped them according to the height of their blood pressure into four groups (Table I).

It will be noted that some conservative method is usually tried first, then a bag or bougie is resorted to. In former years, we often hesitated to use bags or bougies on account of the danger of infection. We feel that these infections were chiefly of an endogenous character and since using vaginal instillations before and after such procedures, our incidence of morbidity and infection has been greatly lessened. Cesarean section was not resorted to very often, only eleven times in this series and then in four instances there were other indications besides the toxemias to make cesarean section the method of choice. In view of some unusually long labors and an occasional loss of the fetus, we feel that in the primipara at term, in the future a more radical procedure is indicated. You will note that infundin is rather freely used in helping along the induction. In view of the recent work of Anselmino, Hoffmann and Kennedy, calling to our attention the posterior pituitary factor in eclampsia, it might be suggested to us that the use of infundin in these cases should be with caution in order to avoid further overaction of this material, particularly in producing spasms of the arterioles and further impairment of the kidney function. Cushing has recently called attention to the finding

TABLE I. CASES OF PREECLAMPSIA, 1930-1933

BLOOD PRESSURE 160-170		BLOOD PRESSURE 170-180		BLOOD PRESSURE 180-190		BLOOD PRESSURE 190-200	
Total Wd.	78	Total Wd.	37	Total Wd.	22	Total Wd.	37
Total P.	19	Total P.	13	Total P.	12	Total P.	13
Grand total	97	Grand total	50	Grand total	34	Grand total	50
Rest Spont. 1	57	Rest Spont. 1	32	Rest Spont. 1	16	Rest Spont. 1	17
Rest Spont. 1 Glucose	17	Rest Spont. 1 Glucose	1	Rest Spont. 1 Glucose	5	Rest Spont. 1 Glucose	7
Rest Induction	22	Rest Induction	15	Rest Induction	10	Rest Induction	21
C.O.Q.	13	C.O.Q.	7	C.O.Q.	4	C.O.Q.	5
Infundin	8	Infundin	5	Infindin	6	Infindin	6
Bag	5	Bag	4	Bag	1	Bag	12
Bougie	2	Bougie		Bougie	1	Bougie	2
Ther. abortion	1	Ther. abortion		Ther. abortion	1	Ther. abortion	1
Memb. Rupt.	1	Memb. Rupt.	2	Memb. Rupt.		Memb. Rupt.	
Rest Cesarean	1 (Myoma)	Rest Cesarean	2 (Vag. scar)	Rest Cesarean	3 (Myoma)	Rest Cesarean	5 (Cont. Pelvis)
Deaths:							
Mothers	0	Mothers	0	Mothers	1	Mothers	0
Babies total	6	Babies total	3	Babies total	8	Babies total	11
Babies premature	4	Babies premature	1	Babies premature	7	Babies premature	9

Preeclamptic Summary, 1930-1933

Total number of cases	231
Maternal mortality	1 case or 0.4%
Total fetal mortality	28 cases or 12 %
Viable fetal mortality (2500 gm. or more)	7 cases or 3 %

of basophilic cells in the posterior portion of the pituitary gland in cases of hypertension and eclampsia as well. Smith and Kunkel of St. Louis have been reviewing this work and to date are not impressed with the constancy of these findings in hypertension, and in one case of eclampsia which was rather thoroughly studied, no basophilic infiltration could be found at all. In view of the fact that infundin has been rather freely used in such a series as this, without any apparent damage, it would seem to indicate that the part the posterior portion of the pituitary gland plays in the etiology of the late toxemias and eclampsia needs definite confirmation.

REFERENCES

(1) *Adair, F. L., and Dieckmann, W. J.:* Trans. Am. Gynec. Soc., 1933 and AM. J. OBST. & GYNEC. **26:** 530, 1933. (2) *Anselmino, K. J., Hoffmann, F., and Kennedy, W. P.:* Edin. M. J. **39:** 376, 1932. (3) *Cushing, H.:* Arch. Int. Med. **51:** 487, 1933. (4) *Peckham, C. H., and Stout, M. L.:* Johns Hopkins Hosp. Bull. **49:** 225, 1931. (5) *Schwarz, O. H.:* Am. J. Surg. **3:** 440, 1927. (6) *Schwarz, O. H.:* Trans. Int. State P-G Med. Assn. N. A., p. 59, 1931. (7) *Schwarz, O. H., and Dorsett, E. L.:* South. M. J. **23:** 288, 1930. (8) *Stander, H. J.:* Davis' Obstetrics and Gynecology **1:** Chap. VIII. W. F. Prior & Co., Inc.

DISCUSSION

DR. WILLIAM A. THOMAS.—We applied bodily, at Presbyterian Hospital, the procedure of nephritic examination to all patients with toxemias from the prenatal clinic, hospitalizing them for single or repeated periods, hoping to reexamine them months later. The usual metabolic, chemical, and liver function tests were employed.

No combination of tests proved as valuable in predicting the course of toxemias as the clinical findings. Especially unreliable was the urea clearance test, since commonly cases with low tests were carried to uneventful term, while some of the favorable clearance cases became eclamptic. Liver function tests seem valuable in a positive way; if low, trouble usually follows. But some patients with normal liver function tests developed toxemic symptoms.

We differentiated cases essentially nephritic, which with low sodium, high potassium, fairly high protein diets, and magnesium sulphate intravenously, were usually controlled, and toxemic or preeclamptic requiring glucose, preferably subcutaneously, which did not respond to magnesium sulphate.

In eclampsia we meet a problem similar to that in nephritis, of a toxin or toxic process which may take one of a number of forms depending, in eclampsia, on whether irritation or damage is greatest in liver, capillaries, pituitary, adrenal, etc. Tissues become hydronephritic, blood water is reduced, anuria results from lack of free water rather than from damaged renal function. Favorable action of glucose is enhanced by partial covering with insulin.

We are attempting to learn how far patients can be carried, and the extent of permanent damage from so carrying them, especially in afteryears. Most cases seen are nephritic, and few are toxemias of pregnancy. The former, if untreated, become uremic, the latter eclamptic. Many are metabolic and circulatory overloaded women whose hearts and capillaries are inadequate for the increased load of pregnancy plus normal activity. They respond admirably to rest and vasomotor tonics.

It is difficult to continue believing in a kidney of pregnancy. The pictures by Fahr are no different from those of Addis and others illustrating Bright's disease, except they seem to be more acute. Nephritis is a degenerative disease, and the fundamental changes in morphology and function are not strictly limited to specific causes.

Furthermore, the liver lesions described as characteristics of eclampsia are frequently absent in that condition.

What I wish to emphasize is that the whole picture of nephritis, in pregnancy or not, is one of generalized tissue damage, with the liver, central nervous system, and endocrine system involved. If we can get away from too fixed a focus, such as kidney or liver, we will progress in treatment of these diseases.

Dr. WILLIAM J. DIECKMANN.—Comments have been made that we have not learned very much about the toxemias of pregnancy, but I believe that blood and urine examinations have definitely been of value and that our knowledge is slowly increasing. In a period of nine years I have had unusual opportunities to examine, study, and treat at least 700 toxemic patients, of whom 75 had eclampsia. Prior to 1934, we had examined 3,688 samples of blood from some 400 toxemic patients. About 2,000 specimens of urine from approximately 300 patients have also been analyzed. We have learned more by repeated examinations on the same patient than by single observations on a large number of patients. I believe that we can make the following statements witlt assurance:

The alterations in blood and plasma volumes in eclampsia and preeclampsia are identical, thus linking these two conditions together and definitely separating them from the patients with nephritic toxemia or essential hypertension. The edema in

the toxemias of pregnancy is not due to a low serum protein, for practically all of the patients have a serum protein above 5 gm. per cent. Despite the high blood pressure, edema, albuminuria, and other signs of kidney involvement, we found the nonprotein nitrogen was 40 mg. per cent or more in only 67 blood specimens from approximately 20 patients. The toxemia is not due to a retention of urea, uric acid, creatinine, or amino acids. The acid-base balance is altered slightly, but because of compensatory changes there is no danger, as a rule, of acidosis or alkalosis. With the exception of hemoglobin, the routine determination of all blood constituents is useless. Each patient presents a different problem, and if chemical examination of the blood is thought advisable, specific determination should be made.

Various renal function tests have been made, and we believe that the test, to be of any value, should be made weeks or even months after delivery.

Approximately 7 per cent of the patients admitted to the Chicago Lying-In Hospital showed evidences of definite toxemia. The treatment, as a rule, should be active and not radical, i.e., little can be gained if the patient has toxemia early in pregnancy in carrying her on to term. The fetal mortality is high in toxemic patients, and we believe permanent damage is done to the mother's cardiovascular system if the pregnancy is permitted to continue too long.

I believe that we will always have toxemias of pregnancy, but proper rest, elimination, and diet will reduce the incidence. Preconceptional, prenatal, and postnatal care are of the utmost value in lowering the incidence and mortality of toxemia.

The mortality due to the toxemias of pregnancy will not be decreased until a rational campaign, even more widespread than that devoted to cancer, is instituted. The public will then become cognizant of the extreme importance of the toxemias of pregnancy, and funds and material will become available for study. Because of the relative scarcity of patients, the research work will have to be carried out in the various cities and districts in specified hospitals, according to designated plans suggested by a central organization, whose membership may be composed of men selected by the various medical schools and special obstetric societies. Thus, within the period of one or two years, all of the various types of therapy can be tried out and the most efficacious instituted with a resultant decrease in mortality. Similarly, the various theories as to the etiology can be investigated on a scale large enough to indicate their value. Within ten years the cure, cause, and prevention of eclampsia and allied toxemia would be known.

DR. CARL W. APFELBACH.—I have been asked to discuss the toxemias of pregnancy from the pathologic standpoint, and have chosen to limit my descriptions to the eclamptic lesions of the kidneys and liver. In addition to the changes already described by Dr Schwarz, I wish to mention the work of Bell who came to the conclusion that the characteristic changes in eclampsia are represented by thickening of the capillary loops of the glomeruli due chiefly to alterations in the basement membrane and hyalinization of portions of the thickened loops. An interpretation of the significance of these changes becomes fairly clear from our general concepts of Bright's disease. Reduction in the size of the kidneys probably does not lead to the nephrotic syndrome and arterial hypertension. For the cause of these symptoms a search must be made elsewhere in the bodies than the kidneys. The changes that result from renal insufficiency were described by Dr. Jensen and myself on the basis of experimental work in which the glomeruli of dogs were infarcted by charcoal particles injected into the renal arteries. Edema and arterial hypertension were not part of experimental renal insufficiency.

So far as the alterations in the liver in eclampsia are concerned it is now generally conceded that there are two types. In some patients there are only retrogressive changes in the hepatic cells. The second type, the characteristic one, was

described by Schmorl and Lubarsch many years ago and is represented by dilatation of the venous sinusoids at the peripheries of the lobules, occlusion of these vessels together with branches of the portal system by fibrin, hemorrhage into the surrounding portions of the lobules, and necrosis of the hepatic cells. The significance of the hepatic lesions in eclampsia will be better deciphered when specific functional tests of the liver are adequate to determine partial destruction of the liver. There does not seem to be any definite correlation between the extent of the changes in the liver and the "eclamptic attack."

DR. JOSEPH B. DELEE.—In the last two years since there has been introduced into the Chicago Lying-In Hospital a new phase of conservatism, I have been able to compare the results of conservatism with the previous treatment which was more active. There has been some improvement in the results in the hospital, but this is due to the use of glucose.

The reasons are plain why throughout the world conservative treatment of eclampsia produces better results than active. In the first place, the majority of eclamptics are in the hands of general practitioners and surgeons and all they know is to empty the uterus. If the man is a surgeon he does a cesarean section. Since cesarean section has a natural mortality due to the tendency of these women to have infection, the percentage of deaths is very high. Furthermore, they do the old classical cesarean section which is a notoriously bad method of treating eclampsia. Finally, from the anesthesia the woman gets bronchopneumonia. So the causes of death are either bronchopneumonia, nephritis, peritonitis, or infection.

DR. RUDOLPH W. HOLMES.—I have taught for many years that the most important fact in the conservation of pregnant women and their infants was conscientious prenatal care. One of the most unjust of criticisms of the medical profession has resulted from the lay public having been deluded into believing that toxemias of pregnancy were among the definitely preventable diseases, and the profession has been the one to foster this erroneous notion. They are no more preventable than are the toxemias of men, or women outside of pregnancy, the nephritides, or any other ailments of mankind. Every obstetrician has his quota of toxemias in patients whom he has supervised from the onset of pregnancy. The fundamental thing to be recognized is that adequate prenatal care will permit the physician to anticipate serious complications, and therefore, prevent serious complications. And, nowhere in the range of medicine are the rewards so gratifying as in the late toxemias.

Cesarean section is the worst method of handling a woman in convulsion, for it destroys at least four or more times as many women as conservative methods. Further, cesarean section should not be the method of choice in treating toxemias without convulsion: timely induction of labor will offer infinitely less risk, will anticipate lethal complications, and does not have the high mortality rate that section has in nonconvulsive toxemia.

DR. BEATRICE TUCKER.—Dr. Dieckmann has asked me to give the statistics on eclampsia from the Chicago Maternity Center. Of 5,486 confinement cases cared for, eclampsia occurred ten times. This is at the rate of one in every 548 cases, or 0.182 per cent. There were 896 primiparas, and 4,590 multiparas. Two primiparas had eclampsia, 0.22 per cent. Eight multipara developed the disease, 0.174 per cent. Thirty per cent of the eclamptics were colored, 70 per cent were white. Two patients were registered for prenatal care at the Chicago Maternity Center. One was a transient. Seven had received prenatal care at various stations throughout the city. In only one patient was the antepartum care adequate. Most of the patients had not been to the clinic within four to six weeks of the time they delivered. Two per cent had antepartum eclampsia; 1 per cent intrapartum eclampsia; 7 per cent

postpartum eclampsia. Two patients died, one at home, and one at Cook County Hospital. The mortality rate was 20 per cent, and all had spontaneous deliveries. There was one stillborn baby.

DR. JOSEPH L. BAER.—Some eight or ten years ago I became interested in microscopy of the capillaries. My hope was that we would be able to distinguish between the preeclamptic patient with what was described as angiospasm and the patient who had a preexisting lesion which had already permanently distorted the capillaries. As time went by I became convinced that the picture we see is too confusing to make this method of differentiation reliable. I think it is accepted that the convulsion itself is not an edema phenomenon but an angiospastic phenomenon.

DR. SCHWARZ (closing).—I cannot agree with Dr. Thomas that the lesions in the kidney in toxemias of pregnancy and especially eclampsia are similar to those that are seen in other kidney conditions. Several years ago I spent six months in Fahr's laboratory going over his material not only on eclampsia but on Bright's disease in general. From the study of Fahr's material, I was definitely convinced that this lesion which he calls pregnancy nephrosis seen in eclampsia is very definitely an entity in itself. Simple nephrosis shows similar changes in the tubules as are seen in eclampsia, but in simple nephrosis the glomeruli are usually uninvolved. What we have in addition to simple nephrosis in eclampsia is the peculiar swelling of the glomeruli. I believe in cases of chronic nephritis in pregnancy either due to previous acute glomerular nephritis or a sclerosis, the increased impairment in pregnancy is due to the fact that remaining functioning tissue becomes involved by a lesion similar to that seen in eclampsia.

Concerning Dr. Baer's remarks on the condition of the capillary, several years after Baer's work, Heynemann felt he could predict, from changes in the capillary circulation, whether a preeclamptic under treatment was getting worse.

Poljanskaja, A. N.: The Rational Treatment of Mastitis and Fistulas of the Breast by Means of Diathermy, Monatschr. f. Geburtsh. u. Gynäk. **97**: 44, 1934.

The author maintains that diathermy gives better results than other forms of treatment in the early stages of mastitis and in cases of stubborn breast fistulas. Diathermy hastens abscess formation of chronic processes and subsequent granulation of the wound. This form of therapy also decreases the pain associated with breast abscesses. It not only shortens the process of healing and restores the function of the breast, but it also produces a much better cosmetic result than other forms of treatment. The average number of treatments in the author's cases was between twelve and fifteen.

J. P. GREENHILL.

VENTRICULAR CEREBRAL HEMORRHAGE IN THE NEWBORN INFANT*

A Pathologic and Etiologic Study of Twenty Cases

Frederick A. Hemsath, B.S., M.D., New York, N. Y.

(From the Departments of Pathology of the New York Lying-In Hospital and the New York Nursery and Child's Hospital)

AMONG the various types of intracranial hemorrhage found in the stillborn and newborn infant, subdural hemorrhage is perhaps best known and its relation to excessive intracranial stress is well established. This study concerns a lesion of greater rarity, hemorrhage into the cerebral ventricles. In this pathologic and etiologic study of 20 consecutive cases observed at autopsy certain facts have been assembled bearing on the question as to whether ventricular hemorrhage should be classed, etiologically, among those intracranial lesions resulting from birth trauma.

These 20 cases were noted among 414 autopsies performed by the author on fresh stillbirths and newborn deaths during the past four and a half years. There were 376 autopsies from the New York Lying-In Hospital, May, 1929 to August, 1932, and 40 from the New York Nursery and Child's Hospital, July, 1932 to December, 1933.

Of the 20 infants, one was stillborn. Among the deaths, the length of life varied from one and one-half hours to four days, with an average of twenty-six hours. In 4 cases the infants were normal for a period of from two hours to twenty-four hours after delivery. In only one case did spontaneous hemorrhages elsewhere in the body indicate hemorrhagic disease of the newborn. As to sex, 14 were males and 6 females, an inequality which might be of interest were the series larger. In 16 cases the hemorrhage was profuse, extending at least to the cisterna magna, and in four cases it was slight, not extending beyond the ventricle of origin.

METHODS

The brain was exposed and removed, after examination of the trunk, by the original method of Beneke.[1] When hemorrhage was present in the third ventricle the lateral ventricles were examined after formalin fixation. This procedure provided satisfactory museum specimens (Figs. 1 and 2) but did not permit accurate determination of the source of hemorrhage. Accordingly the technic was altered by examining the lateral ventricles in all autopsies immediately upon removal of the cerebral hemispheres, the ventricles being entered with blunt curved scissors be-

*Read (by invitation) before a meeting of the New York Obstetrical Society, December 12, 1933.

tween the fornix and thalamus and portions of the medial wall of the lateral ventricle excised to permit clear inspection of the choroid plexus in situ and the floor and lateral wall. The location and extent of hemorrhage beneath the ependyma was clearly discernible by this procedure and the source of free hemorrhage, when

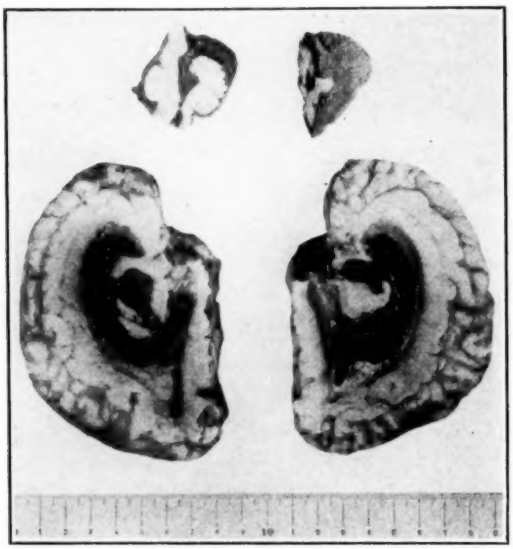


Fig. 1.

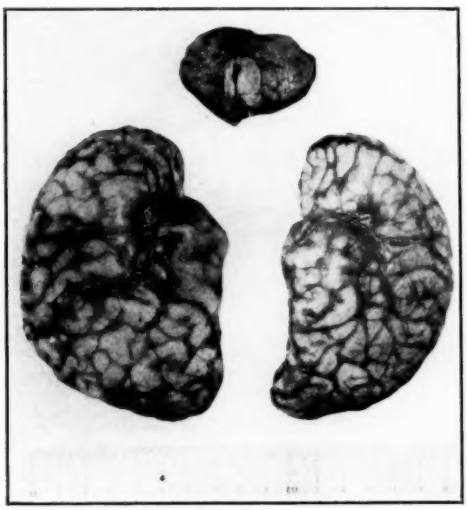


Fig. 2.

Fig. 1.—Case 4. Blood clot in the ventricles, extending to the cisterna magna and surrounding the pons and medulla oblongata.

Fig. 2.—Case 4. Subarachnoidal hemorrhage in the Sylvian fissure is the only cerebral cortical indication of the ventricular hemorrhage .

present, was determined by gentle washing. The fourth ventricle was exposed by sagittal incision.

Subdural cerebral hemorrhages and lacerations of the falx cerebri and tentorium cerebelli were always recorded as to location and extent

but only the gross figures are used because they adequately serve the purpose of the charts. Fatalities were classified as deaths when the heart was beating after delivery or movement of voluntary muscles occurred, even though respiratory movements might not have been made.

INCIDENCE

A partial list of reports from various countries, Table I, shows an autopsy incidence of ventricular hemorrhage from 2.2 per cent to 8.5 per cent, the author's series showing 4.8 per cent. Its incidence with relation to other intracranial hemorrhages, as variously reported, is shown in Table II. In the author's series its frequency, as found at autopsy, was about one-fifth that of subdural cerebral hemorrhage.

TABLE I. AUTOPSY INCIDENCE OF VENTRICULAR HEMORRHAGE

AUTHOR		YEAR	NO. OF AUTOPSIES	VENTRICULAR HEMORRHAGE	
				NO.	PER CENT
Weyhe[2]	Kiel	1889	959	21	2.2
Kowitz[3]	Kiel	1914	2,114	128	6.0
Warwick[4]	Minneapolis	1919	36	3	8.3
Browne[5]	Edinburgh	1921	200	17	8.5
Yagi[6]	Japan	1929	144	9	6.2
Cruickshank[7]	Glasgow	1930	800	58	7.2
Author	New York	1933	414	20	4.8

TABLE II. AUTOPSY INCIDENCE OF VARIOUS INTRACRANIAL HEMORRHAGES

AUTHOR	WEYHE	KOWITZ	YAGI	CRUICKSHANK	AUTHOR
NO. OF AUTOPSIES	959	2,114	144	800	414
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Subdural	8.3	16.7	30.6		21.2
Subarachnoidal	5.9	12.0	9.0		5.4
Intracerebral	3.7	2.9	3.4	1.6	1.4
Ventricular	2.2	6.0	6.2	7.2	4.8

PATHOLOGY

Table III shows that ventricular hemorrhage originated most frequently in the author's cases from subependymal hemorrhages which

TABLE III. ORIGIN OF VENTRICULAR HEMORRHAGE IN TWENTY CASES

Rupture into lateral ventricle of subependymal hemorrhage	7 cases
Dual origin from subependyma and choroid plexus	4 cases
Choroid plexus	2 cases
Massive intracerebral hemorrhage	1 case
Origin not determined	6 cases

Hemorrhage from the choroid plexus in all cases was slight; that from the subependyma was profuse. In seven other cases (not included in this report) there was gross subependymal hemorrhage without rupture into the ventricle.

extended into the lateral ventricles through rupture of the ependyma. Most striking and perplexing was the fact that these subependymal

hemorrhages were found always in much the same location near the anterior portion of the stria terminalis, as illustrated by Figs. 3 and 4. Ruckensteiner and Zöllner[8] have found embryonal tissue in this area in 14 cases of subependymal hemorrhage, half of which extended into the ventricles.

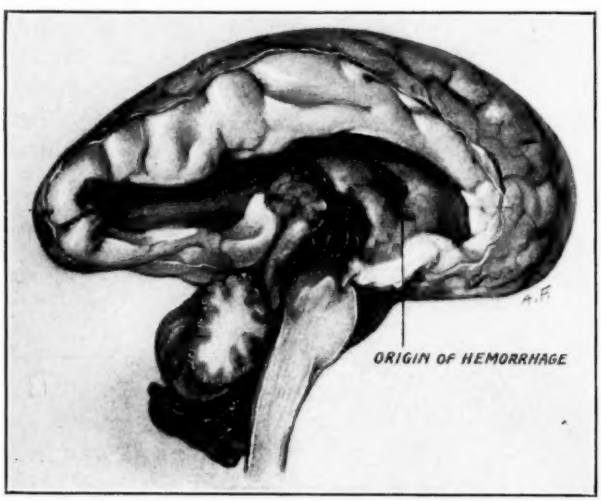


Fig. 3.—Case 8, Triplet I. Drawing showing the origin of ventricular hemorrhage from subependymal hemorrhage near the anterior portion of the stria terminalis. The ventricle was exposed before fixation and the free clot removed by washing.

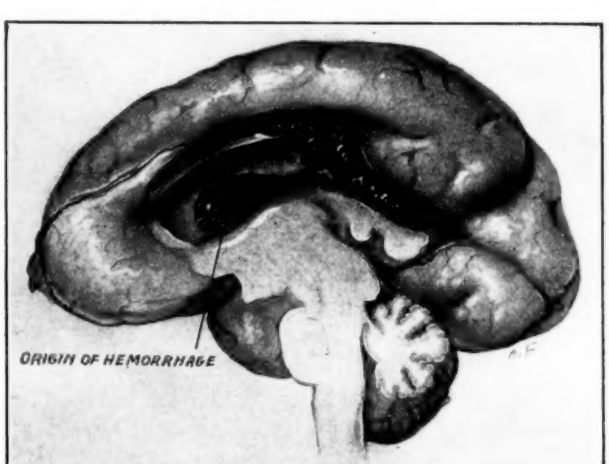


Fig. 4.—Case 8, Triplet II. Drawing showing the origin in the same area as in Fig. 3. The clot in the posterior horn is free hemorrhage. In this and the preceding drawing the portrayal of the convolutions is semidiagrammatic because of the edema. The midbrain and hind-brain have been delineated for the sake of orientation.

This area was examined microscopically in only one case of this series. The infant (Case 14) showed a development of about nine lunar months. The low power microphotograph, Fig. 5, shows in the subependymal zone an enormous number of cells which, by their perivascular concentration, present a picture suggesting en-

cephalitis. Higher magnification, however, shows that these are embryonal neuroglia cells. This cellular area was less than a centimeter in diameter and sharply circumscribed, and it probably constitutes a retention of the embryonal character of the subependymal zone.[9] It is obviously impossible to draw any conclusions or make any

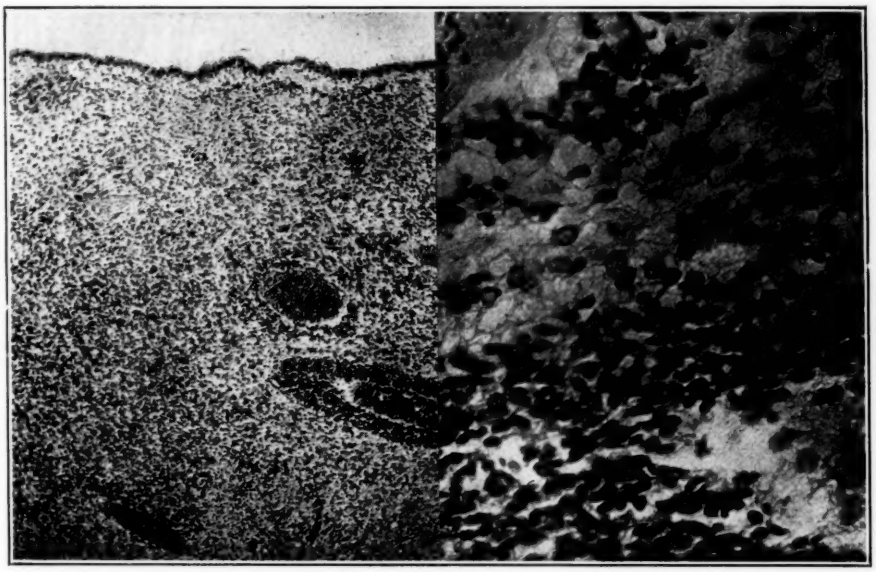


Fig. 5.—Case 14. Low power and high power views of the subependymal zone, lateral wall of the lateral ventricle, coronal section at the level of the tuberculum anterius thalami, showing diffuse subependymal gliosis.

Fig. 6.—Case 18. Medial aspect of the right cerebral hemisphere with the medial wall of the lateral ventricle excised anterior to the sulcus centralis. The blood clot shown occupied the cavity in the medial aspect of the occipitotemporal lobe, which communicated directly with the posterior horn of the lateral ventricle. The hemorrhage in the lateral ventricle has been removed by washing.

generalizations from one case until a large number of normal brains have been examined. The case is presented as an example of the findings of Ruckensteiner and Zöllner in the hope that it will stimulate an interest in the study of this portion of the fetal brain.

Case 18 (Figs. 6 and 7) illustrates a different type of lesion with ventricular hemorrhage arising from a large clot-filled cavity in the brain substance which communicated with the lateral ventricle. The smooth, pale, translucent walls of the cavity indicated hemorrhage into a preexisting area of ischemic softening which possibly antedated the onset of labor since the child died on the third day. Beneke and Zausch[10] have reported a similar case with death on the twelfth day and Cruickshank[7] has seen a number of cases in which the ventricular hemorrhage was associated with extensive destruction of brain tissue.

ETIOLOGY

The 20 cases in this series have been analyzed with respect to etiology under the subdivisions of predisposing causes and inciting causes.

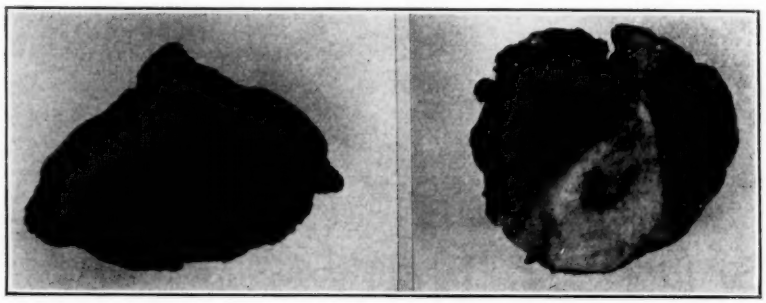


Fig. 7.—Case 18. Two views of the cerebellum showing, on the left, the marked pressure cone and, on the right, large clots occupying smooth-walled cavities in the midperipheral portions of the cerebellar lobes.

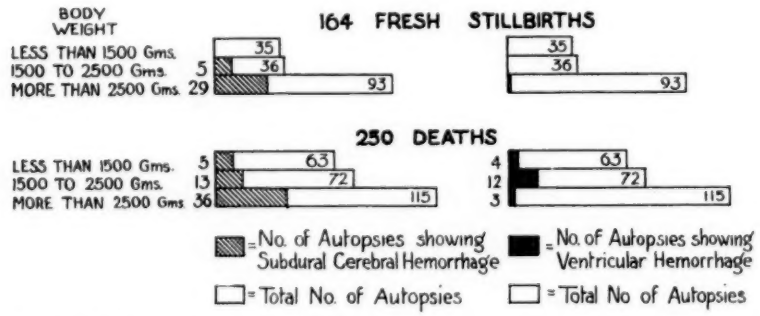


Chart 1.—Subdural cerebral hemorrhages versus ventricular hemorrhages with relation to body development.

In Charts 1, 2, and 3 the 414 autopsies of this series have been classified as to stillbirth or death and the groups further divided according to development. The cases showing subdural cerebral hemorrhage and those showing ventricular hemorrhage have been allocated to their respective groups in Chart 1, showing that ventricular hemorrhage, in contradistinction to subdural cerebral hemorrhage, is essentially a lesion of prematurity. Ylppö[11] found ventricular hemorrhage almost universal in fetuses weighing about 1,000 gm., the frequency decreasing as maturity was approached. Browne[5] says

one does not expect to find ventricular hemorrhage in full-term infants. Expressed conservatively, the greater frequency of ventricular hemorrhage in premature infants indicates a developmental factor as the predisposing cause of the lesion.

In searching for the inciting cause of ventricular hemorrhage the cases have been analyzed with respect to various theories; the first, that ventricular hemorrhage is caused by the venous congestion of deep asphyxia. Petechiae of the thymus, visceral pleura or visceral pericardium, the so-called asphyxial hemorrhages, are universally accepted as indications of asphyxial venous congestion and when present

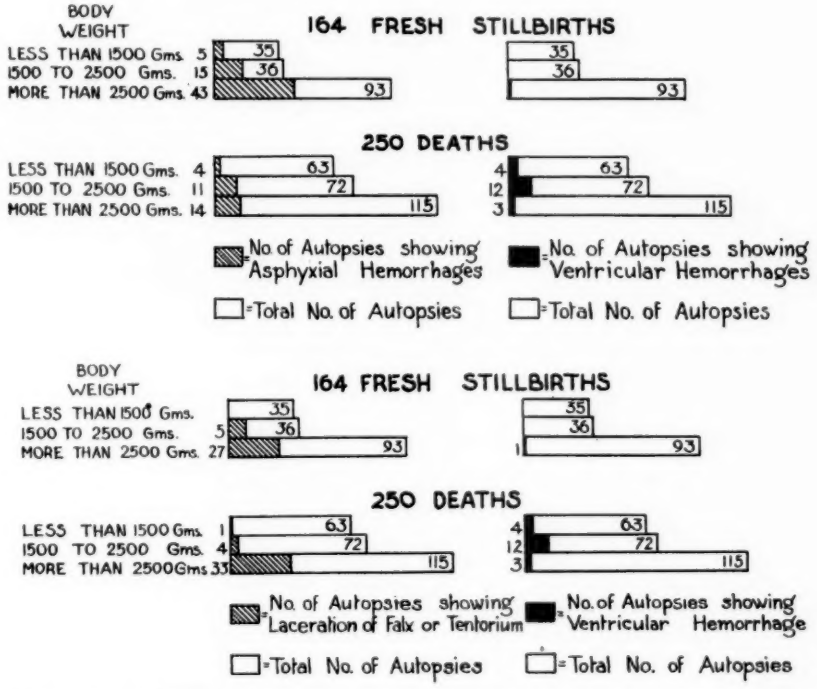


Chart 2.—Asphyxial hemorrhages versus ventricular hemorrhages with relation to body development.

Chart 3.—Lacerations of falx or tentorium versus ventricular hemorrhages with relation to body development.

were always recorded in the author's autopsies. In Chart 2 their occurrence is plotted with relation to that of ventricular hemorrhage. The absence of parallelism is striking. Moreover, among the 250 deaths, 29 cases or 11.6 per cent showed asphyxial hemorrhages while among the 19 deaths showing ventricular hemorrhage, 3 cases or 15.7 per cent showed asphyxial hemorrhages, indicating merely a coincidental association of the two lesions.

In a similar manner the association of excessive intracranial stress has been studied by plotting the cases showing lacerations of the falx cerebri or tentorium cerebelli in Chart 3. Again the graphs are dis-

similar. Among the 250 deaths, 38 cases or 15.2 per cent showed lacerations of the falx or tentorium while among the 19 deaths showing ventricular hemorrhage, 3 cases or 15.7 per cent showed lacerations of the dural membranes, an association only coincidental. Caution is urged in the evaluation of the foregoing statistical analyses because of the potential error due to the comparison of groups markedly unequal in size.

The duration of labor, shown in Table IV, was of average length in the majority of cases. The types of delivery of the 20 cases are shown in Table V. The four cases of ventricular hemorrhage in

TABLE IV. DURATION OF LABOR

First and second stages:	
Less than 5 hours	4 cases
From 7 to 16 hours	10 cases
Over 18 hours	3 cases
Second stage:	
Less than one-half hour in five of the ten cases in which the time was recorded.	

TABLE V. TYPE OF DELIVERY

Spontaneous (70 per cent of the 20 cases):	
Vertex, occiput anterior	12
Vertex, occiput posterior	1
Breech, precipitate	1
Forceps:	
Low	1
Mid B	1
Primary breech extraction	3
Version and breech extraction	1

mature infants in this series were all spontaneous vertex deliveries. In Browne's[5] 17 cases all except one were spontaneous deliveries and in the author's series 70 per cent of the deliveries were spontaneous. A lesion, 70 per cent of whose instances occurred in spontaneous deliveries, does not suggest birth trauma as an etiologic factor unless we assume the predisposing cause to be of such dominant influence that the inciting factor might be furnished by the ordinary course of normal labor. The history of triplets in the author's series (Case 8, Table VI), all of whom showed extensive ventricular hemorrhage, illustrates the importance of a constitutional factor in etiology and the seeming nonassociation of the type of delivery. In this connection also should be noted the case of Gautret and Renon.[12] A fourth child weighing 2,540 gm., delivered spontaneously, was normal until the fourteenth day when it developed convulsions and it died on the fifteenth day. Extensive ventricular hemorrhage was the only lesion found at autopsy.

DIAGNOSIS

Not being a clinician I am reluctant to mention diagnosis and treatment. From my analysis of these cases I would say that with signs

of cerebral hemorrhage manifest, following a spontaneous delivery, ventricular hemorrhage should be suspected.

CASE HISTORIES

The following case histories are those referred to in the text or illustrations.

CASE 4.—H. W., a twenty-seven-year-old, white, gravida iv, primiparous woman registered in the Antepartum Clinic of the Indoor Department of the New York Lying-In Hospital three weeks before delivery. She had one living child four years of age. The two other pregnancies terminated in miscarriage at one and one-half and two months' gestation. Her pelvic measurements, blood pressure, and urine examinations were normal. The Wassermann and Kahn tests were negative. The patient delivered spontaneously after a total labor of two hours, the presentation being vertex, right occiput anterior. The membranes ruptured spontaneously during the first stage of labor. The cord was not about the neck. The patient received no medication prior to or during delivery. The child, a male weighing 2,900 gm., cried vigorously at birth and during the first day. It nursed well. On the second day it became cyanotic and was given oxygen. Feedings were gavaged. It died after forty hours. (Only the pertinent autopsy findings are given.) Body length was 48 cm. Examination of the trunk was negative aside from pulmonary congestion. The cranium showed sutures open and anterior fontanel measuring 20 by 23 mm. The falx and tentorium were intact and there was no subdural hemorrhage. The brain was of normal consistency with well-developed convolutions and flattened sulci. Figs. 1 and 2 illustrate the ventricular and subarachnoidal lesions. The lateral ventricles were opened after formalin fixation and the source of the ventricular hemorrhage was not determined.

CASE 8.—(Triplets.) J. P., a twenty-two-year-old, Italian-born primigravida was admitted on the Indoor Department of the New York Lying-In Hospital at the onset of labor. She had a borderline flat pelvis with a true conjugate of 9½ cm.

TABLE VI. CERTAIN DATA FROM THE HISTORY OF TRIPLETS, ALL OF WHOM SHOWED VENTRICULAR HEMORRHAGE ORIGINATING FROM FOCI OF SUBEPENDYMAL HEMORRHAGE AND EXTENDING TO THE CISTERNA MAGNA

	SEX	WEIGHT GRAMS	BODY LENGTH	PRESENTATION	DELIVERY	DEATH
I	F.	1,350	40.3 cm.	Vertex L.O.A.	Spontaneous	20 hr.
II	M.	1,700	43.2 cm.	Vertex R.O.A.	Version and extraction	37 hr.
III	F.	1,400	41.0 cm.	Transverse	Extraction	22 hr.

The blood pressure was normal. Wassermann and Kahn tests were negative. The first stage of labor lasted sixteen hours during which time she received morphine gr. ¼. Infant I was delivered spontaneously after one hour of second-stage labor, presentation vertex, left occiput anterior. Membranes of infant II were then ruptured, the presentation being vertex, right occiput anterior. The head engaged but did not descend after twenty minutes of active labor consequently delivery was effected by internal podalic version and breech extraction. Infant III presented transversely. The feet were brought down and the infant extracted. Artificial respiration was required for resuscitation of all three infants. Their sex, lengths, weights, and hours of death are given in Table VI. At autopsy the falx and tentorium were intact in all and in none was there subdural cerebral hemorrhage. All showed marked edema of the pia-arachnoid with small areas of hemorrhagic

effusion. In I and III the subependymal hemorrhages were unilateral; in II bilateral and symmetrical, the clots measuring 14 by 8 by 3 mm. The lungs in all were poorly aerated. There were no other lesions. These triplets, according to the standards of Williams[13] developed from three different ova, the placentas showing separate, nonanastomosing circulations.

CASE 14.—D. G., a twenty-seven-year-old, colored West Indian woman, gravida ii, was admitted to the New York Nursery and Child's Hospital near the termination of the first stage of labor which had lasted about eleven hours. Her first pregnancy terminated in abortion at five months' gestation. Her blood pressure was normal. The pelvis was classified as flat. The presentation was frank breech and the delivery was spontaneous precipitate. The infant's condition at birth was rather poor with weak cry and labored respiration. There were 20 c.c. of maternal blood given intramuscularly. There was much mucus and the child was cyanotic at times. Oxygen and carbon dioxide mixture was given almost continuously and the condition seemed to improve until the eighteenth hour. Spinal tap showed 2,000 red blood cells per c.mm. Death occurred at twenty-three hours. At autopsy the body weight was 2,300 gm., the length 43 cm. The lambdoid, sagittal and coronal sutures averaged 8 mm. in width. The anterior fontanel measured 5 cm. in length and 3 cm. in width. The right temporal suture measured 8 mm., the left 3 mm. The right parietal bone showed a thin lower border with a complete fracture 4.3 cm. in length parallel to, and 2 cm. above, the temporal suture. The falx and tentorium were intact aside from a hematoma 1.5 cm. in diameter in the posterior portion of the falx cerebri. The occipital bone showed separation of the squamous and lateral portions without displacement. There was no subdural hemorrhage and, over the cerebral convexities, no subarachnoidal hemorrhage. The brain showed poorly developed convolutions and gapping sulci. Blood clot was present in all the ventricles, aqueduct of Sylvius and cisterna magna, the left lateral ventricle being least involved. The hemorrhage apparently originated from a subependymal hemorrhage near the anterior portion of the stria terminalis in the right lateral ventricle. The microscopic picture of this area has been described in the text. Examination of the trunk was negative aside from cardiac dilatation and poor aeration of the lungs.

CASE 18.—This case was under the care of the Lobenstine Midwifery Clinic and I am indebted to Dr. M. D. Laird, resident obstetrician, for a complete history of delivery and course of the child until its admission to New York Nursery and Child's Hospital. The salient points of the history are as follows: The infant was the third child of a young white Porto Rican. The first child, weighing 10½ pounds died soon after delivery. The second child was a 12-pound, stillborn hydrocephalic. The mother during her second pregnancy had a positive Wassermann reaction which was negative during the last pregnancy. The labor, of three hours' duration, was a spontaneous vertex delivery complicated only by a double coil of umbilical cord about the neck which had to be clamped and cut. The child, weighing 9¾ pounds, was normal for seven hours when it had a choking spell, following which nursing was less vigorous and a gradually increasing somnolence ensued. The child became jaundiced. The first of several convulsions occurred at the age of seventy-two hours. The infant was admitted to New York Nursery and Child's Hospital. It had a weak cry and showed regular respirations, a bulging anterior fontanel, increased tonus of the right extremities, jaundice, a bloody spinal fluid, a clotting time of twelve minutes, and a prolonged bleeding time. There was bleeding from the nostrils. Death occurred three and one-half days after delivery. Autopsy showed a moderate degree of omphalitis, extensive alveolar hemorrhage in the lungs, and a moderate amount of blood in the stomach and intestines. The liver and spleen were normal in size and there was no evidence of syphilis. The brain showed the ventricles

moderately dilated with fluid blood and soft blood clot which extended to the basal cisternae and spinal cord, and originated from a clot-filled cavity in the medial aspect of the right occipitotemporal lobe and communicated with the right lateral ventricle. This clot was quite firm and the walls of the cavity were smooth, pale, and translucent. Two similar clot-filled cavities were present in each lobe of the cerebellum (Figs. 6 and 7).

SUMMARY AND CONCLUSIONS

Twenty cases of ventricular hemorrhage found at autopsy in stillborn and newborn infants are analyzed with reference to pathology and etiology. One case presented a pathologic picture distinct from the rest of the group with the hemorrhage originating from a large clot-filled cavity in the brain substance. The character of this cavity suggested a preexisting area of ischemic softening which may have antedated the onset of labor. Of the 19 other cases, in the majority, profuse hemorrhage originated from subependymal foci near the anterior portion of the stria terminalis of the lateral ventricles, and in a smaller percentage a minor degree of hemorrhage involved the choroid plexus of the lateral ventricles. A developmental factor is apparently a predisposing cause and of great importance in the production of the lesion. The author has not been able to determine any common inciting factor in his cases, most of which were spontaneous vertex deliveries.

Thanks is due and hereby extended to the Clinical Staff of the New York Lying-In Hospital and New York Nursery and Child's Hospital for the privilege of reviewing the clinical records, and to Dr. H. J. Stander, Dr. J. A. Harrar, and Dr. H. C. Williamson for very helpful suggestions.

REFERENCES

(1) *Beneke, R.:* München. med. Wchnschr. **57:** 2125, 1910. (2) *Weyhe, E.:* Inaug. Diss., Kiel, 1889. (3) *Kowitz, H. L.:* Virchows Arch. f. path. Anat. **215:** 233, 1914. (4) *Warwick, M.:* Am. J. M. Sc. **158:** 95, 1919. (5) *Browne, F. J.:* Edinburgh M. J. **27:** 153, 1921. (6) *Yagi, H.:* Japan. J. Obst. & Gynec. **12:** 335, 1929. (7) *Cruickshank, J. N.:* Med. Research Council, Spec. Rep. Ser. No. 145, London, 1930. (8) *Ruckensteiner, E., and Zöllner, F.:* Frankfurt. Ztschr. f. Path. **37:** 568, 1929. (9) *Canavan, M. M., and Hemsath, F. A.:* To appear in Am. J. Dis. Child. (10) *Beneke, R., and Zausch, F.:* Zentralbl. f. Gynäk. **44:** 34, 1920. (11) *Ylppö, A.:* Ztschr. f. Kinderh. **20:** 212, 1919. (12) *Gautret and Renon:* Bull. Soc. d'obst. et de gynéc. de Paris **20:** 195, 1931. (13) *Williams, J. W.:* Obstetrics, ed. 6, New York, 1931, D. Appleton & Co., p. 438.

161 WEST SIXTY-FIRST STREET

DISCUSSION

DR. OSCAR M. SCHLOSS (by invitation).—Intraventricular hemorrhage is probably the rarest and severest form of intracranial hemorrhage in the newborn. I have seen three cases in which intraventricular hemorrhage was found postmortem without having been suspected during life. In all three, however, a diagnosis of intracranial hemorrhage had been made. In one of these the hemorrhage arose from the choroid plexus; in the others the origin was undetermined.

Two other infants who recovered showed signs which were interpreted to indicate intraventricular hemorrhage, although for obvious reasons the diagnosis was not admissible of direct proof. In both cases the onset was sudden, in one eight hours and in the other seventy-two hours after birth. Both infants became extremely

prostrated with livid color. The pupils were contracted in both. The only neurologic signs were convulsions in one and involuntary muscular movements involving all extremities in the other. In both the fontanel was bulging. In one of the patients lumbar puncture showed only a few drops of bloody fluid but on ventricular puncture, pure blood was obtained from the right ventricle. After transfusions and two ventricular punctures, the infant recovered from the immediate symptoms but developed hydrocephalus, due probably to blockage by clot somewhere in the ventricular system. Ultimately the hydrocephalus was arrested, but the child now has symptoms pointing to injury of the basal ganglia.

In the other patient the first lumbar puncture yielded about 15 c.c. of apparently pure blood. Subsequent lumbar punctures were dry, despite the bulging fontanel and other signs of increased intracranial pressure. Pure blood was obtained by ventricular puncture with relief of signs and symptoms of pressure. This patient showed apparently complete recovery with no residual symptoms.

It has always seemed a difficult matter to differentiate clearly the respective rôle of trauma and hemorrhagic diathesis in the etiology of cerebral hemorrhage of the newborn. We know that each can be separately or jointly responsible, but I believe that hemorrhages of solely traumatic origin are much less frequent than is commonly supposed. It seems difficult to explain on this ground many of the cases which have their onset as late as the third day of life. Although unsupported by conclusive histologic evidence, it seems possible that congenital vascular defects or early vascular injuries may be of importance.

It is fortunate that we know a great deal more about treatment than about etiology. The only remedy of definite efficacy that we have is transfusion, and I think transfusion should be given early, particularly if any hemorrhagic manifestations are present. I have seen on a number of occasions a child suffering from hemorrhage from the intestinal tract or from other sources in which transfusion was delayed because the hemorrhage was mild, or an intramuscular injection of blood was given as a temporary measure, only to see within the course of twenty-four or forty-eight hours or more the occurrence of definite signs of intracranial hemorrhage.

Petrignani and Pichevin: Post Operative Psychosis, Bull. Soc. d'obst. et de gynéc., p. 176, March, 1934.

A case of postoperative psychosis following a supracervical hysterectomy for a fibroid uterus is reported. General anesthesia was used. The authors mention that Le Dentu reported 68 cases of postoperative psychoses. Of this number 30 followed gynecologic operations. Among the factors advanced to explain postoperative psychosis are heredity, acquired cerebral insufficiency due to trauma or infection, cerebral shock due to severe injury, insufficiency of the sympathetic system, and postoperative insufficiency of the endocrine glands.

One fact was important in the author's case; namely, that the patient was extremely worried and anxious before the operation. She believed that she would not recover from the anesthetic or that she would develop a thrombosis. These fears persisted during the first few days following the operation.

J. P. GREENHILL.

TREATMENT OF UTERINE HEMORRHAGES DUE TO BENIGN LESIONS, WITH RADIUM AND ROENTGEN RAYS*

HENRY SCHMITZ, M.D., CHICAGO, ILL.

IN 1928 the etiology and treatment of uterine hemorrhages were discussed by me from observations on 2,184 consecutive gynecologic patients. Seven hundred and seventy or 35.29 per cent bleeding uteri were found. The hemorrhages were divided into: (1) those due to extragenital causes; (2) those due to accidents of pregnancy, labor, and puerperium; and (3) those due to functional and anatomical diseases of the genital organs. It is the last group which will be discussed. Five hundred and eighty-six cases or 75.10 per cent belonged to this group.

The functional and pathologic hemorrhages may be separated into malignant and benign. The malignancies accounted for 184 cases or 23.89 per cent of bleeding uteri and the benign lesions counted 586 or 76.10 per cent. The latter were divided into three groups: (1) Those causing a profuse or prolonged menstrual flow, termed hypermenorrhea. They numbered 350 of the 586 cases or 59.72 per cent. (2) Those characterized by too frequent menstruations or polymenorrhea. They counted 111 cases or 21.35 per cent. (3) Hemorrhages occurring independently of the menses or metrorrhagias. They amounted to 125 cases or 18.93 per cent.

The causes of functional hypermenorrhea were hypoplasia in 27 cases, asthenia in 25 cases, and the menopause in 18 cases. It may be assumed that they are mostly due to functional derangement of ovulation. The functional polymenorrheas due to ovarian dysfunction numbered 35 cases and the metrorrhagias accompanying hemorrhagic metropathies accounted for 33 cases.

The treatment of functional uterine hemorrhages was surgical, radiologic, or medical. The number of hypermenorrheas indicating radiation treatment was 20 of the 73 cases or 27.39 per cent; of the polymenorrheas 3 of the 30 cases or 10.0 per cent; and of the metrorrhagias 22 of 36 cases or 61.10 per cent. Hence in a total number of 149 functional uterine hemorrhages 45 cases or 32.31 per cent were subjected to radiation therapy. Four hundred and thirty-two cases were treated either by medical management or surgery.

There were 145 cases of myomata uteri in the series and 90 of these had as the sole symptom bleeding: 118 or 81.30 per cent were treated surgically; 16 or 11.03 per cent radiologically and 11 or 7.59 per cent medically.

*Read before the Chicago Gynecological Society, February 16, 1934.

The study has been continued in 433 cases of benign uterine hemorrhages that had definite indications for radiation therapy. The group does not include the cases that were relieved by surgical or medical treatment. The survey comprises the clinical data and the results of radiation therapy. The former consist of some aspects of diagnosis, the relation of age, the duration of the bleeding, the influence of pregnancy and labor; while the discussion on radiation therapy includes the methods of irradiation either with radium or roentgen rays, the radiation dose, the results and complications of irradiation.

CLINICAL DATA

The diagnosis without exception should include a thorough anamnesis, a detailed bimanual palpation and a curettage or biopsy. The history may elicit valuable facts as: the type of bleeding, e.g. hypermenorrhea, polymenorrhea, oligohypermenorrhea, polyhypermenorrhea, pelvic infections and benign tumors; the palpation gives information of the mobility, location, size, shape, and consistency of the uterus and adnexa; laboratory examinations will aid in the determination of the blood count, picture and sedimentation time and the virulency test of the cervical secretion; the curettage enables one to determine the physiologic and anatomic pathology, especially hyperplasia of the endometrium; malignancy should always be ruled out or in by microscopic evidence. A bleeding uterus should not be treated unless the cause is positively known, and if this knowledge cannot be obtained from the history and physical examination then diagnostic curettage or biopsy must be done. Based on these facts the 433 cases were grouped as seen in Table I.

TABLE I. THE CAUSE OF BENIGN UTERINE HEMORRHAGES

DIAGNOSIS		NUMBER	PER CENT
Hemorrhagic Metropathies			
a. Juvenile: up to 20 years	10		
b. Mature: from 21 to 35 years	69		
c. Menopause: from 36 to 50 years	174	253	58.50
Senile hemorrhages: 51 years or older		22	5.12
Chronic cervicitis, and bleeding from undetermin able causes		36	8.39
Myomas:			
Up to 35 years	21		
36 years or older	97		
Endometriomas	4	122	27.99

The relation of age to the bleeding uterus may be perused from Table II. The ages were collected for five-year periods. They were separated into those for the bleeding myomas and those for the bleeding uteri. The youngest patient in the myoma group was twenty-seven and the oldest sixty-eight. The youngest patient in the metropathia group was sixteen, the oldest fifty. The maximal fre-

quency was at forty-five years for myomas and at forty-two years for metropathies. The parallelism of the age graphs is apparent. Myomas appear mostly during the mature period of menstrual life; metropathies occur at all ages but most frequently in the juvenile and menopausal periods of life when ovulation is started or begins to ebb. The carcinoma age curve has been added. The maximum frequency of carcinoma uteri is at fifty-five years; more than two-thirds of the cancers appearing between forty-five and sixty years of age. It should always be remembered that no age in a woman's life is free from hemorrhages and that hemorrhagic metropathies, myomas, and carcinomas may occur at all ages.

TABLE II. THE RELATION OF AGE TO UTERINE HEMORRHAGES

PENTADES	UP TO 20	21-25	26-30	31-35	36-40	41-45	46-50	51 AND OVER
Myomas:								
Number			6	8	26	43	16	10
Per cent			9.72	7.09	23.01	38.05	14.17	7.96
Bleeding Uteri:								
Number	10	19	24	35	58	86	43	28
Per cent	3.31	6.29	7.95	11.69	19.21	28.48	14.24	8.83
Carcinomas:								
Number		4	15	42	60	85	85	99
Per cent		0.81	3.33	8.48	12.12	17.17	17.17	20.0

The duration of the bleeding before the admission of the patient has been tabulated in Table III. The numbers are arranged in months during the first half year and for semesters after the first six months. A fair number of women seek medical advice during the first six months of bleeding. Yet it may be stated that patients with uterine

TABLE III. THE DURATION OF UTERINE BLEEDING OF BENIGN ORIGIN

Myomas:												
Semesters	1						2	3	4	5	6	7
Number	32						26	5	18	2	5	25
Months	1	2	3	4	5	6						
Number	9	4	2	5	2	10						
Bleeding Uteri:												
Semesters	1						2	3	4	5	6	7
Number	134						57	10	41		2	53
Months	1	2	3	4	5	6						
Number	17	22	26	17	25	27						

hemorrhages are at least very negligent in seeking medical advice at the very onset of the bleeding. The patient does not realize that she may be suffering from carcinoma. When the worries from the abnormal bleeding subside, if putrid discharges, loss of weight, or pain do not appear, then the patient is likely to postpone medical consultation for years. Corroboration of this statement may be had from the cancer statistics all over our country. Much missionary propaganda

must be done to induce women to seek medical advice at the appearance of uterine bleeding and to impress upon them the necessity of periodic health surveys to prevent such lesions and subsequently hemorrhages.

The incidence of labors in this group is shown in Table IV. Twenty-four or 36.67 per cent of the 122 myomas, and 79 or 24.69 per cent of the 311 benign uterine hemorrhages were in nulliparas. The number of labors in both groups were plotted and compared with the graph obtained from 400 women admitted to the hospital for nongenital diseases. In the latter 73 or 18.25 per cent were nulliparas. Therefore sterility in women who later in life develop a myoma is 100 per cent, and in women who have metropathies about 50 per cent higher than in normal women. Undoubtedly ovarian disturbances are much more frequent at the beginning and termination of menstrual life, and hence changes in the myometrium are more frequent. Ovarian dysfunction and endometrial pathology are responsible for the hemorrhages at these periods.

TABLE IV. THE FREQUENCY OF LABORS IN UTERINE HEMORRHAGES

PARITIES	MYOMAS	METROPATHIES	CARCINOMAS	NORMAL WOMEN
0	36 36	26.33	20.87	18.25
1	14.0	7.66	17.79	14.0
2	16.52	19.0	12.65	15.0
3	18.18	13.66	13.68	18.0
4	4.96	6.65	7.82	10.5
5	2.49	8.0	7.61	7.0
6	1.66	4.0	5.94	4.0
7	2.49	4.67	4.56	4.5
8	2.49	3.33	2.70	3.5
9	0.24	3.66	2.45	1.75
10		1.33	1.45	1.25
11		0.33	1.04	1.0
12		1.0	0.21	0.5
13		1.0	0.63	0.5
14			0.42	0.25
15			0.21	

RADIATION TREATMENT

The treatment of uterine bleeding due to benign lesions should be divided into that for myomas and that for hemorrhagic metropathies and other benign hemorrhages.

The treatment of bleeding myomatous uteri is either surgical or radiologic. Generally the statement may be made that patients not older than thirty-five years and patients older than thirty-five years but desiring offspring should be treated surgically. Myomectomy with the conservation of a functioning uterus is the operation of choice if it can be technically done. Irradiations are indicated in:

1. A bleeding intramural myoma free from adnexal complication, degeneration or malignancy, and located intramurally, in a patient thirty-six years or older.

2. Women younger than thirty-six years who are poor surgical risks due to constitutional complications.
3. Radium may be used in uteri not larger than a first trimester pregnancy, and roentgen rays in myomas of all sizes.

Notwithstanding the painstaking examinations before assignment to the radiation therapy institute 13 myomas, that is 10.74 per cent of the total 122 cases, were treated by operations. An abdominal myomectomy was done in one case, bleeding persisted and 1,200 mg. el. hours radium inserted one year later brought about permanent amenorrhea. In another patient a vaginal myomectomy was done in 1931. The tumor was pedunculated. Microscopic examination revealed a leiomyosarcoma. Radium was immediately used, the dose was 4,200 mg. el. hours applied within fifteen days. The patient is well at the present writing. One patient had an inoperable rectal carcinoma with the uterine myoma. Following the exploratory laparotomy combined radium and roentgen rays were given, but death ensued four months later from intestinal obstruction. Another patient had an intraligamentous ovarian cyst with the bleeding uterus. Nine patients had multilobular uteri with circuitous cavities. Such uteri almost invariably have submucous or subserous tumors and as a rule do not respond to irradiations. As the percentage of uterine myomas treated with irradiations is 17.78 in our series a total of about 600 cases of uterine myomas was treated within a period of twenty years. Radiation therapy was begun in our clinic in 1912.

Radium was used in the uterine myomas 100 times. Treatment was repeated once in six cases: six, seven, and eighteen months and one, three, and ten years later. It was repeated twice in one case, seven and twelve months later.

Operations after irradiation were necessary for uncontrollable bleeding in three cases, three, nine, and twelve months later. In one case a pedunculated myoma was found in the uterine cavity. One patient returned three years later with an inoperable botryoid sarcoma. After the exploratory laparotomy combined radium and roentgen treatments were given. There was one serious morbidity. Three weeks after radium a pelvic abscess was drained through a posterior colpotomy.

Roentgen rays were applied in 17 cases. One patient had a myoma the size of a full-term pregnancy. The treatment was repeated four months later and followed by a permanent amenorrhea.

The combined method of radium and roentgen rays was employed in 7 cases. The doses were the same as used in carcinomas. Four patients had inoperable endometriomas invading the rectovaginal septum. Inoperability was determined by exploratory laparotomies. Three cases were clinically diagnosed as myoma with carcinoma, but microscopic examinations did not concur in the clinical diagnosis.

Therefore in 122 myomata uteri referred for radiation therapy, the treatment was primarily surgical in 13 cases, and secondary operations were necessary in 5 cases after radium treatment. Radium was employed in 85 myomata uteri with a good result in 82 cases or 90.14 per cent. The treatment was repeated once in 6 cases and twice in one case.

Roentgen ray was used in 17 cases and combined roentgen and radium rays in 7 cases. They arrested the bleeding in every case but one. This is explainable by the large doses of rays used. The one failure had a hysterectomy six months later for persistent bleeding.

Failures of radiation treatment were associated with unrecognized pathology contraindicating irradiation, or were due to insufficient dosage. In 26 cases in which the radium dose was 1,800 or more milligram element hours not a single repetition of treatment was necessary nor did bleeding recur.

Three deaths occurred in the series. One death only could be attributed to the treatment, namely a septic peritonitis following dilatation, curettage, and radium insertion. This gives a mortality per-

TABLE V

DOSE IN MG. EL. HR.	NUMBER	REPETITION OF RADIATION	DOSE IN MG. EL. HR.
Radium:			
300	1	6 months later	1200
600	6	18 months	1200
		10 years	1200
		3 years	1200
900	2	1 year	1200
1200	57	7 months and 12 months	1200
1800	10		
2400	9	1 month	1325 R x-rays

Combined Radium and Roentgen Rays:

RADIUM	+	ROENTGEN	NUMBER
2400 to 4000		1325 R Units	7

Roentgen Rays:

DOSE IN R UNITS	NUMBER
150	2
300	1
450	10
900	4

centage of 0.86. If the two malignancies are added then the mortality percentage is 2.48.

The radiation doses applied in the myomas are best recorded in tabular form for the sake of brevity and ease of survey. The small doses were applied in hemorrhages occurring in the mature women thirty-five years or younger to preserve genital function.

The indications for irradiation in the bleeding benign lesions of the uterus are:

A bleeding uterus that has resisted conservative measures of treatment and is not complicated by pelvic infections.

In women of the juvenile period, that is up to twenty years and in mature women of from twenty-one to thirty-five years, temporary amenorrhea should be produced. Roentgen rays are preferable as the dose can be more correctly determined than that of radium rays. Women of the menopause period from thirty-six to fifty and of the senile period from fifty-one up may be treated with either radium or roentgen rays. As the radiation treatment must be preceded by a curettage to rule out malignancy, radium is used by preference. However, radium treatment is almost invariably followed by a profuse watery secretion which may last six months in some cases, especially if a destruction of the internal os has been caused by hydro- or pyometra. Applying radium in the Y-shaped applicator prevents destruction of the mucosa of the internal os and subsequent atresia and retention of secretion is prevented. Roentgen rays act directly on the ovaries and the annoying watery discharges from the uterus are not seen.

In chronic cervicitides and senile metrorrhagias that are clinically malignant but histologically benign it is advisable to give the patient a combined radium and roentgen ray treatment as used in true carcinomas. The desire of the patient for offspring should always be heeded regardless of age. This may require a modification of the radiation dose in order to produce a temporary amenorrhea.

Consternation has been thrown by geneticists into the ranks of gynecologists, here and abroad, about the possibility of injury to the genes or chromosomes of the sex cells by exposure to the rays. Subsequent pregnancies might lead to deficiencies in the development of the fetus, especially microcephaly. If conception did not occur within six months after radiation, Nürnberger, Gauss, and Murphy did not see any deformities; though the investigations of Morgan, Mueller, among others in animal experimentations point to such a possibility. An absolute interdiction of marital relations will prevent early conceptions. A pregnant uterus should not be radiated. If in doubt the Aschheim-Zondek test should aid in the diagnosis.

The temporary amenorrhea dose of roentgen ray is 35 per cent lower than the castration dose. The latter is 450 R units applied to the midpelvis through an anterior and posterior field; hence 300 R measured with back-scatter and produced with 200 kilovolts rotengen rays will produce in mature women a temporary amenorrhea, lasting from nine to eighteen months. The output of transformer and tubes must be standardized with dose meters to attain the expected result. The reoccur-

rence of the menses is usually preceded by menstrual molimina during the last two or three months of amenorrhea period.

The radiation dose and the results and complications of radiation therapy were tabulated to facilitate and shorten a perusal.

Radium arrested bleeding in 294 of the 298 cases. In eight the treatment was repeated after varying periods. In two a hysterectomy was

TABLE VI. RADIATION TREATMENT OF BENIGN UTERINE HEMORRHAGES

MG. EL. HR.	NUMBER	REPETITION OF TREATMENT AND COMPLICATIONS
300	13	Six months later hysterectomy in one case.
600	28	Eighteen months later 1200 mg. el. hr. radium.
900	9	
1200	202	Eight, 6, 7, 8, and 9 months 1200 mg. el. hr. radium. Two hysterectomies for continuous bleeding 4 and 7 months later. One death from sepsis. In two cases, clinically cancerous but not corroborated microscopically, 2400 mg. el. hr. radium plus 1325 R units roentgen were added.
1800	29	
2400	9	
3000	3	To each 900 R units roentgen in one sitting each to an anterior and a posterior field were added as they were clinically carcinoma.
3600	4	All clinically carcinoma.
4200	1	Clinically carcinoma.
Total number	298	
Roentgen Rays Produced With 200 KV		
R Units	*Number*	
300	7	Plus 900 R units four months later in one case.
450	15	Plus 1200 mg. el. hr. radium six years later. One hysterectomy for uncontrollable bleeding. In one case amputation of cervix preceded radiation treatment, one year. Microscopic examination revealed an atypia of epithelium. Six months after radiation treatment bleeding recurred and microscopic examination revealed typical carcinoma; and 4800 mg. el. hr. radium plus 3000 R roentgen at 800 KV were immediately applied.
600	1	
Total number	23	

performed. One patient died from sepsis. Therefore the cure rate was 98.66 per cent. Repetition of treatment was not necessary in a single case treated with 1,800 or more milligram element hours.

Roentgen rays were applied in 23 cases. In 3 cases repetition of treatment was necessary. One hysterectomy was performed for uncontrollable bleeding. In one case carcinoma was found microscopically, though eighteen months previously atypia of epithelial cells was found.

CONCLUSIONS

In this group of uterine hemorrhages, due to benign causes and treated by radiations, about one-fourth were myomas. The incidence of

age shows that myomas occur mostly after the twenty-sixth year; the youngest patient being twenty-seven and the oldest sixty-eight. While uterine hemorrhages occur at all ages, the greatest frequency is between thirty-six and fifty years of age. The same observation that is made in carcinomas of the uterus is also observed in uterine hemorrhages due to benign causes, namely, that the patients do not come for diagnosis at the onset of bleeding.

The frequency of nulliparity in normal women is 18.25 per cent. It is 26.33 per cent in benign uterine hemorrhages and 36.36 per cent in bleeding myomas.

The indications for radiation therapy are given.

The radium dose which assures invariably complete amenorrhea is about 1,800 mg. element hours. If this dose was used, then repetition of treatment was never necessary. If roentgen rays were used, then the dose of 450 R units should be applied, through two fields at the seat of the ovaries. Diagnostic curettage should precede applications of radiation in all cases. If presumptive signs of malignancy are present and microscopic diagnosis does not corroborate the clinical diagnosis, then massive radiations should be employed as recommended for radiation treatment of uterine carcinomas. The good end-results of irradiation in myomas of the uterus were 90.14 per cent. The mortality in myomas was 3. One patient died from a septic peritonitis, following dilatation, curettage, and radium insertion, and two cases showed malignancy, one year and three years afterward, respectively, so that the entire mortality in the myomas was 2.48 per cent. Malignancies after irradiation were seen in less than 1 per cent of the entire group of 433 cases.

In bleeding uteri, the good end-results from radiation were 98.66 per cent. Only one death occurred from septic peritonitis. Radiation therapy is the method of choice in well-selected, uncomplicated cases of uterine hemorrhages, due to benign causes.

REFERENCE

(1) *Schmitz, Henry:* Am. J. Obst. & Gynec. **15**: 344, 1928. J. A. M. A. **91**: 955, 1928.

DISCUSSION*

DR. CARL P. BAUER.—Five hundred cases of fibromyoma uteri were taken seriatim from the Gynecological and Obstetrical Service of the Presbyterian Hospital starting Dec. 31, 1933, and going back four years.

Four hundred fifteen patients were married and 234 had full-term pregnancies; 10 patients had abortions but no full-term pregnancies, and 181 were sterile; an incidence of 43 per cent sterility.

The associated pathology in the sterile group was 61 per cent and in the fertile group 59 per cent. The percentage of associated pathology in the sterile group was as follows: endometriosis 47 per cent; swiss cheese hyperplasia of the endometrium 23 per cent; carcinoma 4 per cent; cystomas of the ovary 6 per cent, and chronic salpingitis 20 per cent. In the fertile group, 48 per cent endometriosis; 38 per cent

*See also p. 416.

swiss cheese hyperplasia; 10 per cent carcinoma and 4 per cent cystomas of the ovary.

Four hundred forty-four patients were operated upon. Three had dilatation and curettement, 18 myomectomy, 18 radium insertion (16 benign and 2 carcinoma of the cervix), 14 total abdominal hysterectomy, 179 supravaginal hysterectomy, and 212 vaginal hysterectomy. The mortality in this series was 1.57 per cent. Two patients having vaginal hysterectomy died, one from intestinal obstruction and one from undetermined cause. Four deaths occurred following supravaginal hysterectomy, one from collapse in a diabetic patient, one from ileus, and two from peritonitis associated with infected fibroids. One patient died from embolism following myomectomy.

CONCLUSIONS

1. Forty-three per cent of 500 cases of fibroids were sterile.

2. The associated pathology with fibroids was about the same in the sterile and fertile groups, except that carcinoma of the cervix was more frequent in the fertile group. The number of cases with associated pathology ran between 59 and 61 per cent. The frequency of the associated pathology may be expressed as follows: Endometriosis, swiss cheese hyperplasia of the endometrium, carcinoma and benign neoplasms of the ovaries.

3. Vaginal hysterectomy seems to be the operation of choice for most of the fibroids in this series.

Cruickshank and Sharman: The Biology of the Vagina in the Human Subject, J. Obst. & Gynaec. Brit. Emp. **41**: 208, 1934.

Extensive observations on the bacterial flora of the vagina at all ages from birth until after the menopause and during pregnancy revealed: 1. Soon after birth and for the first two or three weeks of life a simple homogeneous flora of Döderlein's vaginal bacillus is established in the vagina in association with a highly acid nonpurulent secretion. 2. After the first month of life and throughout childhood until puberty, the bacterial flora is sparse and varied, while the secretion is scanty or absent and, when measurable, alkaline in reaction. 3. At puberty there is a sudden reversion to the type of flora and secretion found in the first week of life. The simple bacterial flora and highly acid secretion apparently persist in the healthy woman until the menopause. 4. Following the menopause there is a return to the sparse flora and scanty alkaline secretion found in the vagina before puberty. These findings correspond with the authors' studies on glycogen in the vaginal epithelium. When glycogen is present in the epithelium as in the newborn infant and during the reproductive period, the homogeneous bacterial flora and highly acid secretion appear. When it is absent, the secretion is scanty and alkaline and the bacterial flora usually varied.

WILLIAM F. MENGERT.

THE VALUE OF POSTOPERATIVE ROENTGEN IRRADIATION IN CARCINOMA OF THE OVARY*

JOHN B. MONTGOMERY, M.D., AND JOHN T. FARRELL, JR., M.D.,
PHILADELPHIA, PA.

IN AN earlier paper[1] we pointed out that due to the multiplicity of factors involved and to the incompleteness of detail in some reports, it is not always possible to compare reports of various authors as to the results of x-ray therapy in carcinoma of the ovary. Our earlier communication reviewed the results obtained in a series of twenty-two patients operated upon on the service of Professor Brooke M. Anspach, at the Jefferson Medical College Hospital, to whom x-ray therapy was administered on the service of Professor Willis F. Manges.

To correlate reported results we have reviewed the literature chronologically and have restudied the 22 cases from the clinical and pathologic points of view in their relation to postoperative roentgen therapy.

From 1912 to the present time a number of investigators have reported almost 1,000 cases of ovarian carcinoma treated by x-ray, radium, or surgery, or a combination of these, with more or less encouraging results.

It would appear, from our review, that postoperative roentgen irradiation has definite value in the treatment of carcinoma of the ovary. However, it is well to point out that in most instances all the factors influencing prognosis were not recorded. It is important if statistics are to be compared that the histologic diagnosis, grade of malignancy, degree of operability, and amount of radiation be stated. We have, therefore, studied our cases in the light of these factors, paying particular attention in this communication to the clinical and pathologic features, as we emphasized the roentgenologic in the earlier one.

HISTOLOGIC DIAGNOSIS

All patients were operated upon and the diagnosis proved by histologic examination of tissue removed. The following histologic types were diagnosed: adenocarcinoma, 4 cases; papillary adenocarcinoma, 3 cases; papillary cystadenocarcinoma, 14 cases; granulosa cell carcinoma, 1 case. The first two types occurred as solid or semisolid tumors of moderate size. The papillary cystadenocarcinomas were usually large serous or pseudomucinous cysts, in which carcinoma had developed. The single granulosa cell carcinoma was found in a moderately large tumor with multiple cystic cavities.

*Read at meeting of the Obstetrical Society of Philadelphia, Jan. 4, 1934.

For lack of space it is not possible to publish the authors' extended review of the literature and complete bibliography, but the complete article will be published in the authors' reprints.

GRADE OF MALIGNANCY

Following the suggestion of H. C. Taylor, Jr., the cases have been divided into three histologic grades of malignancy. The grading of each tissue was done by one of us (J. B. M.) with the assistance of Dr. Baxter L. Crawford, pathologist to the Jefferson Hospital, who had made most of the original histologic studies. The grading was based upon the degree of anaplasia as indicated by the extent of cell differentiation, variation in size and shape of the cells, and nuclear changes.

Each tumor was graded on the basis of the histologic picture alone, no consideration being given to the clinical course in any case.

Low-grade malignancy or Grade I (Fig. 1) includes those tumors in which well-differentiated columnar epithelium lined the glands and

Fig. 1.—Low-grade or Grade I malignancy well-differentiated columnar epithelium; the adult structure is maintained except in occasional areas where early malignant changes are seen.

cysts, the adult structure being maintained throughout except in occasional areas where the cells infiltrated the stroma or formed numerous layers within the glands.

Intermediate grade malignancy or Grade II (Fig. 2) includes those tumors in which the columnar epithelium was not so well differentiated; the individual cells presented variations in size and shape, and moderate nuclear changes with more extensive infiltration and the frequent formation of solid areas. Glandular and papillary structures were poorly developed and distorted.

High-grade malignancy or Grade III (Fig. 3) includes those tumors in which undifferentiated epithelial cells with marked nuclear changes developed in strands or solid areas. There was little evidence of glandular or papillary structure.

CLINICAL CLASSIFICATION

Once a tumor has been definitely diagnosed as carcinoma the extent of the growth is the important clinical factor influencing the prognosis. Recent authors have taken cognizance of this and classified their cases

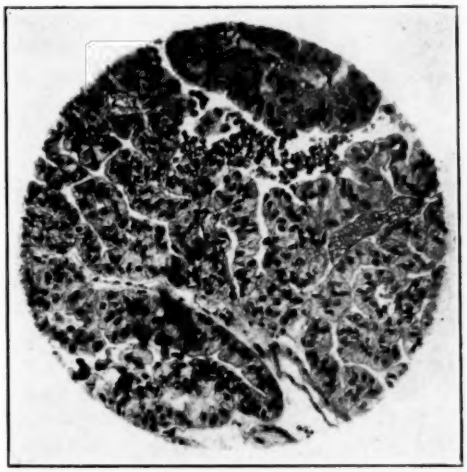


Fig. 2.—Intermediate grade or Grade II malignancy columnar epithelium not so well differentiated. There are variations in size and shape of the cells, nuclear changes, and more extensive infiltration. The glandular and papillary structures are poorly developed.

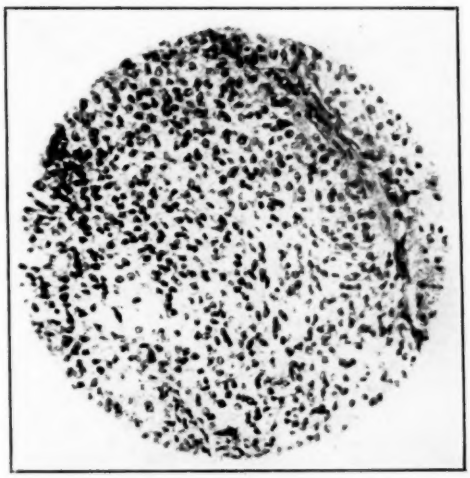


Fig. 3.—High-grade or Grade III malignancy and undifferentiated epithelial cells with marked nuclear changes. Solid carcinoma with little evidence of glandular or papillary structure.

so as to differentiate between early, far advanced, and hopeless cases. Keene, Pancoast and Pendergrass,[3] considered two groups: Group I consisted of widespread carcinoma in which only a laparotomy could be done; Group II included all cases in which a complete or partial operation was possible. Ford[4] reported results in three clinical groups,

unilateral, bilateral, and inoperable. Heyman[5] studied the cases treated at the radiumhemmett as radically operable, incompletely operable, recurrent, and inoperable. Others have used somewhat similar classifications.

We have adopted the following clinical classification based upon Schmitz's method of classifying carcinoma of the cervix.

Group 1: Ovarian carcinoma without extension or involvement of surrounding or adjacent parts, completely operable. This group consists of unilateral ovarian tumors which are not adherent.

Group 2: Ovarian carcinoma with extension or involvement of surrounding or adjacent parts. Completely operable. In this group are placed completely removable bilateral carcinomas, completely removable carcinomas which are adherent, completely removable carcinomas with extension, and Group 1 cysts ruptured during operation.

Group 3: Ovarian carcinoma with extension or involvement of surrounding or adjacent parts. Incompletely operable. This group includes all cases in which a partial operation can be done.

Group 4: Ovarian carcinoma with extension or involvement of surrounding or adjacent parts or with metastasis at a distance. Inoperable cases in which only a laparotomy and biopsy can be done.

Group 5: Ovarian carcinoma, recurrent. Inoperable. The terminal stage of all except those cured.

IRRADIATION

Irradiation was usually begun from two to four weeks after operation. Two methods were used. Prior to August, 1927, massive doses were given in a single sitting at right angles to one of three or four pelvic ports. The amount given was that which the skin would tolerate, and the entire course was completed in three or four days. The factors were 3 milliamperes at 170 to 200 kilovolts, filtered through 0.5 mm. of copper and 1.0 mm. of aluminum, at 50 cm. skin-target distance, through ports 16, 19, or 20 cm. square. An erythema was obtained with 270 milliampere minutes of treatment.

After August, 1927, treatment was given after the saturation method of Pfahler.[6] Usually four ports were used, though occasionally, in thin persons, only three. The patients were measured and a diagram of the pelvis made by the procedures devised by Weatherwax[7] employing Desjardin's[8] charts. Effective depth dosage was measured in international roentgens and a graphic chart kept to show from day to day the amount of radiation received. All patients after January, 1925, received treatment with the following factors: 20 or 30 milliamperes, 175 to 200 kilovolts, filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin-target distance, through ports 16, 19, or 20 cm. square. The central ray was directed obliquely into the pelvis. The erythema value from January, 1925, to August, 1930, was 970 r, and since August, 1930, has been 800 r; in terms of milliampere minutes the erythema

ranged from 320 to 610 milliampere minutes as determined by the efficiency of the tubes employed and the voltage at which they could be operated.

In all instances an effort was made to give the maximum amount of radiation which the skin, pelvic structures, and general condition of the patient would permit. No attention was paid to the histologic type of the tumor, its grade of malignancy, or degree of operability in determining the amount to be administered, because experience with tumors in other areas had shown that these factors could not be used as criteria for the determination of the amount of radiation required.

Patients were treated on alternate days. Each day treatment was given, enough x-ray was administered through each of the four pelvic ports, so that at the end of four weeks the effective depth dose was from 1,600 to 2,000 r. The general condition of the patient sometimes would not permit this. In stout patients these doses could not always be delivered into the depths because of the danger of damaging the skin. Slender patients permitted of the ready administration of the maximum depth dose.

As noted in the review of the literature, radium has been used in association with roentgen irradiation in treatment of these tumors. This is notably true of the patients reported from the Radiumhemmett by Heyman,[2, 5] and by Ford from the Mayo Clinic.[13] Radium was not used routinely by us, only three patients in the series having received radium applications; in two, 2,400 mg. hours were applied through the intrauterine route, and in the other the radium was applied directly through the abdominal incision into the tumor mass. It is obviously impossible to draw conclusions from these three patients.

Patients were watched for lowering of the white blood count, and with the development of an appreciable leucopenia, treatment was stopped. This was infrequent.

Diarrhea was not uncommon; it was not often accompanied by other symptoms. Abdominal pain or tenderness was only rarely associated with irritability of the bowel developing during irradiation. The diarrhea usually disappeared promptly on cessation of the treatment, in fact, it often stopped if treatment was postponed for one day.

While diarrhea as evidence of colitis should be taken into account, it is not an indication for stopping treatment. It cannot be doubted that it is due to irradiation, because it is seen most frequently in thin persons who receive the greatest depth doses.

RESULTS

Histologic Type of Tumor (Table I).—The papillary cystadenocarcinoma was the type most frequently encountered. Of the 22 patients 14 had this variety, 9 were serous, and 5 pseudomucinous. Seven of these patients are alive, 6 dead, and 1 untraced. Four of the living had serous tumors and 3 had pseudomucinous. Four

TABLE I. POSTOPERATIVE ROENTGEN IRRADIATION IN CARCINOMA OF THE OVARY. TYPE OF TUMOR*

		LIVING				DEAD				UNTRACED
		AC	PA	PCA	GCC	AC	PA	PCA	GCC	PCA
Group	1			2				2		1
	2			3						
	3		1	2	1	3		2		
	4					1	2	2		
Total			1	7	1	4	2	6		1

*AC, Adenocarcinoma; PA, Papillary adenocarcinoma; PCA, Papillary cystadenocarcinoma; GCC, Granulosa cell carcinoma.

patients with serous tumors and 2 with pseudomucinous died. The one untraced patient had a pseudomucinous growth.

Four of the 5 patients living for more than five years had papillary cystadenocarcinoma; 3 were of Grade I malignancy, the other of Grade III. These patients represent 80 per cent of the five-year cures.

Adenocarcinoma was the next most frequent; 4 patients had this type and they are all dead. Three of them had incompletely operable tumors, 2 of Grade II malignancy, and one of Grade III. One adenocarcinoma of Grade II malignancy was wholly inoperable.

Papillary adenocarcinoma was encountered in 3 patients, one with an incompletely operable Grade III tumor is alive almost two years after operation with part of the tumor still present. Two patients with this variety are dead. Both had wholly inoperable tumors; one with a Grade III tumor died three months after operation, the other with a Grade II tumor died one year postoperatively.

The one patient with a granulosa cell carcinoma is the fifth in the group of patients cured for five years. This tumor was of Grade I malignancy.

Grade of Malignancy (Table II).—Tumors of Grade I malignancy were the most frequently encountered. Of 10 of this grade, 7 are alive, 2 have died, and one is untraced. The average duration of life to date in those who have survived is thirty-eight months; of the 2 who died the average duration was six and one-half months.

Five patients, all of whom have died, had tumors of Grade II malignancy. Three of them incompletely operable had an average postoperative duration of fourteen months, in two with wholly inoperable tumors the duration of life averaged slightly less than five months.

Of the 7 patients with Grade III tumors 6 are dead and one is living for more than six years. In the latter the tumor was completely operable. Three of those who died had incompletely operable tumors, and in 3 the tumors were wholly inoperable.

Degree of Operability (Tables III, IV, V, and VI).—Five patients had completely operable tumors (Group 1, Table III). All were large cysts of low-grade malignancy. Two with a pseudomucinous type of cyst are alive, one four years and six months, the other two years and two months postoperatively. Two with serous tumors died, both in less than one year. One patient with a pseudomucinous tumor is untraced.

Three patients with completely operable tumors with extension (Group 2, Table IV) are alive more than six years after operation; all of them had papillary cystadenocarcinoma, one with a serous tumor of Grade III malignancy, two with Grade I tumors, one of which was serous and the other pseudomucinous.

Nine patients had only partially removable tumors (Group 3, Table V). Four of them are alive. In 3 the tumor was Grade I, 2 were serous papillary cystadeno-

TABLE II. ROENTGEN IRRADIATION IN CARCINOMA OF THE OVARY. GRADE OF MALIGNANCY

		LIVING					DEAD					UNKNOWN
		GRADE			DURATION AFTER OPERATION		GRADE			DURATION AFTER OPERATION		
		I	II	III	AVERAGE	TOTAL	I	II	III	AVERAGE	TOTAL	
Group	1	2			38 mo.	76 mo.	2			6.5 mo.	13 mo.	1
	2	2		1	81 mo.	244 mo.						
	3	3		1	68 mo.	273 mo.		3	2	14+ mo.	71 mo.	
	4							2	3	5– mo.	29 mo.	
Total		7		2			2	5	5			1

carcinoma, and the third was a granulosa cell tumor; the fourth patient in this group had a Grade III papillary adenocarcinoma. Five patients are dead; in 3 the tumor was Grade II, in 2 Grade III.

Five patients with wholly inoperable tumors are dead (Group 4, Table VI).

TABLE III. GROUP 1. OVARIAN CARCINOMA WITHOUT EXTENSION, COMPLETELY OPERABLE

PATIENT	AGE	TYPE*	GRADE†	TOTAL IRRADIATION			RESULT
				COURSES	SKIN R	DEPTH R	
1 T. M.	29	PCA-p	I	10- 8—10-25-28	1740		Untraced
2 E. L.	22	PCA-p	I	7-11— 7-24-29	1740	2280	Living 4 yr. 6 mo. P. O.
3 T. C.	61	PCA-s	I	11-29—12-23-29	2000	2800	Died 1 yr. P. O.
4 C. P.	47	PCA-s	I	9-29—10-21-31	1200	1680	Died 1 mo. P. O. ulcerative colitis
5 A. M.	60	PCA-p	I	10-10—11-14-31	1360	1360	Living 2 yr. 2 mo. P. O.

*PCA, Papillary cystadenocarcinoma; s, serous; p, pseudomucinous.

†I, Low-grade malignancy. Summary: 5 cases, Grade I: 2, L-1-4 yr. 6 mo. 1-2, yr. 2 mo.; 2, Dead in less than 1 yr.; 1, Not traced.

TABLE IV. GROUP 2. OVARIAN CARCINOMA WITH EXTENSION, COMPLETELY OPERABLE

PATIENT	AGE	TYPE*	GRADE†	TOTAL IRRADIATION			RESULT
				COURSES	SKIN R	DEPTH R	
6 H. R.	57	PCA-s	III	6-26— 6-30-26	1280	1280	Living 7 yr. 5 mo. P. O.
7 M. P.	40	PCA-s	I	8- 4— 8-12-27	1350	1350	Living 6 yr. 5 mo. P. O.
8 M. A.	35	PCA-p	I	8-16— 8-26-27	1740	2440	Living 6 yr. 6 mo. P. O.

*PCA, Papillary cystadenocarcinoma; s, serous; p, pseudomucinous.

†I, Low-grade malignancy; III, high-grade malignancy. Summary: 3 cases; 2 Grade I; 1 Grade III. All living for more than six years.

All died in less than one year; 2 were of Grade II and 3 were of Grade III malignancy. One patient had an adenocarcinoma, 2 had papillary adenocarcinoma, and 2 had papillary cystadenocarcinoma of the serous type.

SUMMARY

Of the entire group of 22 patients 9 are alive twenty-two months or longer. Twelve are dead, one is untraced and for the purpose of this study is counted as dead. In this group of patients who have died are five with inoperable tumors (Group 4, Table VI), none of whom survived operation more than seven months. The average postoperative duration of life was a little less than five months. Five had only partially operable tumors, all of intermediate or high-grade malignancy, and survived operation slightly more than fourteen months. Two patients with completely operable tumors died, one after one month and one after one year.

Palliative Results.—Our experience confirms the observations of Keene, Pancoast and Pendergrass[3] who noted decrease in ascites and lessening of pain in many of their advanced cases where partial excision

TABLE V. GROUP 3. OVARIAN CARCINOMA WITH EXTENSION, INCOMPLETELY OPERABLE

PATIENT	AGE	TYPE*	GRADE†	TOTAL IRRADIATION			RESULT
				COURSES	SKIN R	DEPTH R	
9 M. Y.	32	PCA-s	I	1-29— 2- 2-24	1450	1300	Recurrence May 1932.
				6-13— 8- 9-32	1040	940	Living 10 yr. P. O.
10 F. C.	48	GCC	I	12- 7—12-16-26	1840	1840	Operation Sept. 27, 1926.
				5- 5— 5-13-27	1840	1840	
				4-14— 5-12-31	1480	1480	Recurrence 1930 treated with radium 2400 mg. hr. and x-ray 1931, local recurrence and pulmonary metastasis treated with x-ray 1932. Lived 7 yr. 1 mo. P. O.
				2-21— 3- 2-32	1200	1200	
11 E. F.	60	PCA-p	III	1-28— 4-16-28	1840	2300	
				11-12—11-25-29	730	900	Died 1 yr. 6 mo. P. O.
12 L. C.	56	AC	II	1- 9— 1-22-30	2000	1800	Endometrial carcinoma treated with radium 1927.
				5-26— 6-20-30	2200	2000	Ovarian growth probably secondary. Died 3 yr. 8 mo.
13 M. D.	32	PCA-s	I	3- 1— 3-26-30	2300	2100	Living in good health with evidence of part of growth still present 3 yr. 10 mo. P. O.
				1-25— 2-17-33	900	810	
14 M. M.	44	PCA-s	II	2- 5— 2-11-31	480	480	Died 2 mo. P. O. agranulocytic anemia.
15 J. A.	38	AC	III	1- 7— 2- 3-32	1440	1440	Died 4 mo. carcinoma in huge teratoma.
16 M. H.	41	AC	II	1-21— 2-12-32	960	1350	Died 3 mo. Large ovarian tumor probably secondary to endometrial carcinoma.
17 A. M.	48	PA	III	2-18— 3-11-32	1040	1250	Living 1 yr. 10 mo. with part of tumor still present.

*AC, Adenocarcinoma. PA, Papillary adenocarcinoma. PCA, Papillary cystadenocarcinoma: s, serous; p, pseudomucinous. GCC, Granulosa cell carcinoma.

†I, Low grade. II, Intermediate grade. III, High grade.

TABLE VI. GROUP 4. OVARIAN CARCINOMA WITH EXTENSION, INOPERABLE

PATIENT	AGE	TYPE*	GRADE†	TOTAL IRRADIATION			RESULT
				COURSES	SKIN R	DEPTH R	
18 B. S.	42	PCA-s	III	2- 6— 2-10-24	800		Died 4 mo. P. O.
19 M. C.	46	AC	II	8- 9— 8-15-27	450	540	Died 3 mo. P. O.
20 M. L.	54	PA	III	8-25— 9-17-27	1550	930	Died 3 mo. P. O.
21 A. S.	38	PA	II	7-10— 8- 1-28	1840	1840	Died 1 yr. P. O.
22 H. F.	35	PCA-s	III	11-30—12-19-28	1160	1600	Died 7 mo. P. O.

*AC, Adenocarcinoma. PA, Papillary adenocarcinoma. PCA, Papillary cystadenocarcinoma; s = serous.

†II, Intermediate Grade. III, High Grade. Summary: 5 cases, all died in less than 1 year: 2 Grade II; 3 Grade III.

of the growth was followed by roentgen irradiation. With them we also noted little improvement in the far advanced and inoperable cases.

Five-Year Results (Table VII).—Of the 22, 11 were operated upon and treated with x-ray more than five years ago, 10 have been traced and of these, 5 are still alive. The percentage of five-year cures in this series is, therefore, 45.4 per cent. Three of these patients had wholly operable tumors, 2 of Grade I malignancy, and 1 of Grade III, all were papil-

TABLE VII. POSTOPERATIVE ROENTGEN IRRADIATION IN CARCINOMA OF THE OVARY. RESULTS IN PATIENTS SEEN MORE THAN FIVE YEARS

	PATIENTS	GRADE OF MALIGNANCY I	II	III	LIVING 5 YEARS OR MORE	DEAD	UNTRACED
Group 1							
	5 T. M.	1					1
Group 2							
	6 N. F.			1	7 yr. 3 mo.		
	7 M. A.	1			6 yr. 3 mo.		
	8 M. P.	1			6 yr. 3 mo.		
Group 3							
	9 M. Y.	1			10 yr.		
	10 F. C.	1			7 yr.		
Group 4							
	18 B. S.			1		1	
	19 A. C.			1		1	
	20 M. L.			1		1	
	21 A. S.			1		1	
	22 H. F.			1		1	
Total	11	5		6	5	5	1
Per cent					45.4	54.6	

TABLE VIII. FIVE-YEAR RESULTS IN 14 CASES TREATED BY OPERATION ONLY

GROUP	PATIENT	MALIGNANCY I	II	III	LIVING 5 YEARS OR MORE	DIED
1	L. E.	1			1	
	H. G.		1			P. O. D.*
2	S. T.	1			1	
3	E. S.			1		6 mo.
	L. W.			1		6 mo.
	E. L.			1		3 mo.
4	S. E.	?	?	?		7 mo.
	K. S.	?	?	?		2 mo.
	J. R.			1		Not traced
	D. H.			1		3 mo.
	J. B.			1		7 mo.
	G. I.			1		P. O. D.
	J. P.			1		6 mo.
	M. A.			1		12 mo.

*P. O. D, Postoperative death.

lary cystadenocarcinomas, 2 of the serous and 1 of the pseudomucinous type. In 2 of those who have survived for more than five years, the tumors were only partially operable. One with a granulosa cell carcinoma is now suffering from a recurrence. The other, a papillary cystadenocarcinoma of the serous type and of Grade I malignancy, operated

upon and irradiated ten years ago is now living and well eighteen months after the partial removal of a recurrent growth.

Ovarian Carcinoma Treated by Operation Only (Table VIII).—During the time the patients whose case histories comprise this study were being treated with operation and irradiation, 14 patients with ovarian carcinoma were treated by operation alone. More than half were in clinical Group 4. Two patients with low-grade malignancy are living for more than five years. One was in Group 1 and one in Group 2. One patient has not been traced, two died following operation and all others died within six months.

CONCLUSIONS

1. A comparison of the results of treatment in various series of reported cases of ovarian carcinoma is difficult because of the lack of uniform data.

2. If accurate statistics as to the efficacy of any treatment are to accumulate, it is important that the histologic type of tumor, its grade of malignancy, degree of operability and the amount of irradiation administered be noted in case reports.

3. A method for the clinical classification of ovarian carcinoma is outlined.

4. Twenty-two cases of ovarian carcinoma have been analyzed according to type, grade of malignancy, operability and response to postoperative roentgen irradiation. Of eleven patients observed for more than five years, five, or 45.4 per cent, are alive.

5. Fourteen patients had papillary cystadenocarcinoma, 7 are living, and 7 dead; 3 patients had papillary adenocarcinoma, one is living, and 2 are dead; 4 patients with adenocarcinoma are dead; one patient with a granulosa cell carcinoma is living.

6. In order of malignancy the granulosa cell is the least malignant, the papillary cystadenocarcinoma the next, the papillary adenocarcinoma is more malignant than the preceding and the adenocarcinoma the most malignant.

7. The histologic grading of malignancy is important in the prognosis of ovarian carcinoma. Only one patient whose tumor was of high-grade malignancy has survived for more than five years. All others with tumors of intermediate and high grades of malignancy are dead. Those with tumors of the intermediate grades lived longer than those in whom the malignancy was of a high grade.

8. The more completely operable the tumor the greater the life expectancy.

9. Postoperative roentgen irradiation is often of value in relieving pain and ascites and in reducing the size of the tumor.

10. Comparison of this series of patients treated with postoperative

irradiation and a group treated by operation alone indicates that the duration of life is longer in the irradiated patients.

11. Nearly all patients with ovarian carcinoma, regardless of the hopelessness of the prognosis, where the general condition permits, should have postoperative irradiation.

REFERENCES

(1) *Montgomery, J. B., and Farrell, J. T., Jr.:* Radiology **23**: August, 1934. (2) *Heyman, J.:* Helsingfors **3**: 109, 1924. (3) *Keene, F. E., Pancoast, H. K., and Pendergrass, E. P.:* J. A. M. A. **89**: 1053, 1927. (4) *Ford, F. A.:* AM. J. OBST. & GYNEC. **5**: 16, 1928. (5) *Heyman, J.:* Acta Radiol. **13**: 329, 1932. (6) *Pfahler, G. E.:* Brit. J. Radiol. **31**: 45, 1926. (7) *Weatherwax, J. L.:* Physics of Radiology, New York, 1931, Paul B. Hoeber, Inc., p. 143. (8) *Desjardin, A. U.:* Anatomic Cross Section Charts of the Human Trunk, New York, 1921, Paul B. Hoeber, Inc.

DISCUSSION

DR. FLOYD E. KEENE.—Our experience with irradiation in the treatment of carcinoma of the ovary corresponds very closely with the results which Dr. Montgomery has reported and seemed to warrant the conclusion that in some instances, irradiation was of distinct palliative value. Dr. Payne and Dr. Harris are now engaged in reviewing the results from irradiation during the past seven years and they are even more encouraging, doubtless due to improved technic and equipment.

Of the 55 patients treated in the Radiological Department, 17 were eliminated for one reason or another, leaving 38 for analysis. Based upon the extent of the disease, these patients can be divided into 3 groups: (1) advanced lesions with peritoneal carcinomatosis in which the primary growth could not be removed; (2) removable growths but peritoneal metastases present; and (3) the early cases where the growth could be completely excised and there was no visible evidence of extension. Twenty-one patients are dead and all belong to Groups 1 and 2. In 90 per cent of these death occurred two years or less after the beginning of their treatment. Expressed in another way, this study shows that if the patient belonging to Group 1 or 2 lives for two years after irradiation has been given, her chances are 90 per cent good for one or more years of life.

It is impossible to prophesy what the response to irradiation will be in any given case. In our experience, the histologic type has been of little or no value in prognosis. In evaluating the effects of irradiation, the results must be judged from the standpoints of palliation and cure. Of the latter, we cannot speak. Under palliative effects are included prolongation of life, lessening of ascites, relief of pain and diminution or disappearance of the abdominal masses. In 60 per cent, pain was lessened or entirely relieved. Ascites was present in 22 patients and in one-third of these accumulation was retarded, thus lengthening the interval between tappings and in a few, it was entirely checked. Abdominal masses were reduced in 30 per cent and in some, they completely disappeared for a time. These results seem to justify the conclusion that x-ray irradiation is of value as a palliative measure.

Twenty-six patients were treated two or more years ago and 10 of these are alive at the present time. In Group 1, there were 7 patients, one of whom is still living; more than five years have elapsed since her first treatment was given. Of the 15 patients in Group 2, 5 are still alive. Of the 4 patients in Group 3, all are living and apparently free from any demonstrable evidence of malignancy.

Our experience has shown that even in the presence of peritoneal metastases, the primary growth should be removed whenever possible. The advisability of combining deep x-ray therapy with operation in the early cases is still controversial, but

the evidence at hand strongly indicates that by combining the two, the total five year salvage will be increased.

B. P. WIDMANN.—Regressions from a palliative standpoint have at times been so phenomenal that I believe irradiation as a routine procedure is justified particularly when the physical condition of the patient will tolerate intensive treatment. Many of my own observations of apparently good results are totally lacking in the important factors of correlating age, duration of involvement, and microscopic cellular grading, etc. I agree with Dr. Keene that the question of cellular differentiation of tumors cannot be regarded as absolute evidence as to the possible radiosensitivity or radioresistance of the particular case. This evidence is often misleading. There is frequently a great difference of opinion with experienced histologists as to how a tumor should be graded, but there is a greater possible error that may result from the acceptance of a tumor grading on tissue removed from one surface or margin as compared to another region of the growth. The duration of the growth and the anatomical site may control the variable cellular characters. This information coupled with the approximate extent of involvement and other factors must be correlated very methodically to serve as criteria against which a known dosage of x-ray treatment can be evaluated from the standpoint of end-results. There has been delayed progress in the radiation treatment of malignant disease of the ovary because the majority of these cases in the past have been fairly widespread in the extent of involvement by general abdominal metastasis. This widespread involvement necessitates a distribution of radiation over large fields. The experience which is practically uniform everywhere shows that abdominal radiation involves the possibility of much radiation reaction (nausea, vomiting, etc.) This occurred in individuals supposedly in good physical condition considering the approximate extent of involvement. This complication has frequently instigated the withdrawal of radiation and is probably the one factor which has led to more failures because of undertreatment than any other combination of factors. In many instances the question of undertreatment has always been considered as a possible source of failure. Our experience has shown that many of these cases seem to show progressive failure even as late as after an apparent thorough and adequate second series of high voltage x-ray treatment, but very decided response after additional treatment. The improvement in health and strength as well as a definite regression of the palpable abdominal masses and a complete inhibition to the further development of fluid is a very common observation. At the Philadelphia General Hospital we have not discovered anything that will control radiation reaction. Intravenous glucose and sometimes normal saline seem to have been beneficial. We have not observed anemia to be a contraindication to radiation, patients with red cell counts as low as 2,000,000 and hemoglobin as low as 25 and 30 per cent will tolerate radiation given cautiously. On the other hand a white cell count less than 3,000 seems to be the most decided contraindication. We believe it is worth while considering transfusion in the very profound anemias. There is an occasional but very transient benefit. Repeated transfusions have apparently shown no special benefit.

JOHN T. FARRELL, JR.—I believe this study confirms the opinion of Drs. Keene and Widmann that all patients with ovarian carcinoma should be given the maximum roentgen dosage possible within the limits of safety. In patients with completely operable tumor life may be prolonged, those with extensive involvement with a tumor of a high degree of malignancy may respond to the extent that life may be made more comfortable and possibly lengthened.

The amount of irradiation to be given is to be determined not by the histologic type of tumor, its operability or degree of malignancy, but by the patient's response as far as the symptoms and signs are concerned.

RADIUM METHODS AND STATISTICS OF CANCER OF THE CERVIX*

H. S. Crossen, M.D., St. Louis, Mo.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine and Barnes Hospital)

IN THE continual search for improvement in the treatment of cancer of the cervix uteri, gynecologists welcome help from every source. If there is any modification of method that will really give the patient a better chance to survive, we wish to use it. However, our hopes have so often been raised by claims that later proved to be mistaken that any change from a tried and reliable method must be made only after critical analysis has shown definitely the superiority of such modification.

Considerable attention has been drawn for some years to the method of radium treatment developed by Dr. Regaud at the Radium Institute of Paris. His statistics have shown a high cure rate, and a modification of the method has been used extensively in this country. The theory of the method is to give to each generation of cancer cells a dose of radium at the stage of cell division when they are most radium-sensitive, and this is supposed to be accomplished by spreading the dosage over from five to seven days. Recently an excellent worker from the Washington University Medical School, who spent several months making a detailed study of French radium and x-ray methods in general, returned quite enthusiastic about this particular method of treating cancer of the cervix. Also, in a recent article by Healy of New York, attention is called to the high percentage of cures shown in Regaud's series. So it seems desirable, in the interest of possible change in that direction, to review the results of that and other methods of radium treatment.

The methods of irradiation which have been used for cancer of the cervix are so many and so varied that the subject is confusing. The present methods are variations of earlier ones, which must be understood to some extent in order to appreciate those now in use. A starting point and basis for classification of methods may be obtained by a brief review of our work at the Washington University Medical School. About 1920, we felt at the Barnes Hospital of the Medical School that radium treatment of cancer of the cervix had reached a stage where it should be considered for the operable cases. Taking up the matter in a systematic way and getting all the information we could from literature and from visiting in the East, where radium was being used, we decided that radium

*Read before the St. Louis Gynecological Society, January 12, 1924.

treatment as then developed was the best treatment for all cases of cancer of the cervix except the very earliest.

The next question to decide was as to the method of irradiation to employ. After careful consideration, we decided on giving the full radium dosage in a single treatment. Supplementary x-ray treatment also was to be employed, in the hope of devitalizing scattered cancer cells beyond the reach of the radium.

The plan adopted was consistently followed for a period of ten years. There were three reasons for holding steadily to this plan in spite of the many other methods and modifications proposed. First, the plan was adopted only after critical consideration of the whole situation; second, with this disease several years of trial are required to determine the real curative value of a method; and, third, careful study of the other plans proposed from time to time convinced us that they did not offer any better, if as good, chance of cure. In 1931 an analysis was made of the five-year cases, that is, of the patients treated in the years 1921-26. This gave a five-year series of 121 cases which had been handled by a uniform plan of treatment. This analysis and the conclusions from it and from the subsequent five years of work, were presented at the American Gynecological Society in 1931.[6]

The advisability of this plan of treatment was amply supported by the results of our ten years' experience and by the literature of the period. About a year ago we adopted two modifications. The first was to include the earliest cases in the regular irradiation treatment. All cases are now treated by irradiation, any operation required for a special condition being only supplementary to the irradiation. The second modification was to give a part of the x-ray therapy before the radium application, with the idea of securing some devitalizing effect on the marginal cancer cells before the stir-up of the radium implantation in the center of the mass. This had been used by Healy with decided benefit, especially where there was a large papillary mass or ulceration at the vaginal vault. In the interval vaginal douches and applications, when needed, aid in putting the cancerous area in safer condition for the radium application.

Regaud's method is based upon a very attractive theory of treatment. However, considering the various factors involved, it is a question whether this attempted fine adjustment of radium application to the phases of cancer cell division will prove superior in practical results. The necessity of a careful consideration of all factors in this complicated problem is illustrated by the experience of a leading gynecologist in New York who hoped to graduate the radium dosage so as to devitalize cancer cells without causing sloughing of normal tissue, the calculation as to dosage being based upon elaborate study of cell reactions. The plan seemed to work well, and he and his associates were enthusiastic about

the pliability of the healed vaginal vault and the absence of destruction of the cervix. After using the method for some years he presented a paper[7] at the American Gynecological Society on follow-up and reradiation in cancer, and to emphasize the importance of the latter he called attention to the fact that in his series of cases nearly 50 per cent of the patients needed reradiation. In the sharp discussion which followed, it was brought out that his remarkable percentage of reradiations was due to insufficient primary radiation and that there was not this recurrence in series where adequate radiation was given in the beginning of treatment.

In judging which method of irradiation is best, we must still depend largely on results attained. There are so many factors about which little is known that it is hazardous to depend very far on theory, no matter how attractive. In trying to determine whether or not Regaud, with his spread-out method timed according to the stages of cancer cell division, obtained results definitely superior to the results of other methods, I compared the published series from the following representative institutions.

Radium Institute of Paris (Regaud and Lacassagne). *British Medical Journal*, November, 1932. This article[1] shows the five-year results from 1919 to 1926. The cases are divided into two groups of four years each, the last group showing the cases for the years 1923-1926. A great advance over previous percentage of cures was attained in 1923, when the five-year survivals reached 31 per cent. In 1924, 35 per cent was attained; in 1925, 32 per cent; and in 1926, 35 per cent. Taking these four favorable years for the representative series, there is a total of 317 cases with 107 five-year survivals—33.7 per cent.

Woman's Hospital of New York (Ward and Farrar). *Surgery, Gynecology and Obstetrics*, February, 1933. This article[2] shows the grouped results from 1919 to 1927, without division into years. There were 343 patients receiving treatment, with 85 five-year survivals—24.7 per cent.

Memorial Hospital of New York (Healy). *Journal of the American Medical Association*, December, 1931. This article[3] contains an analysis of the cases from 1918 to 1926, the work being started by Dr. Harold Bailey in 1915. There were 1,574 patients with 352 survivals—22.3 per cent. There was no separation into years so that a group of the later years could be taken. The nearest approach to this was a previous report[4] of the work of 1924, comprising 150 patients with 30 survivals (20 per cent).

Howard A. Kelly Hospital of Baltimore (Burnam). *Surgery, Gynecology and Obstetrics*, February, 1933. This article[5] shows the results from 1911 to 1927. As in Regaud's series, the period comprising the last four years was selected as being most representative for the method employed. In this series (1924-1927) there were 349 cases with 70 survivals—20 per cent.

Barnes Hospital of St. Louis (Crossen and Newell). AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, October, 1931, and same Journal, August, 1932. These articles[6] show the results from 1921 to 1926. The series comprised a total of 121 patients, 27 of whom were found at that time alive and free from recurrence, and 15 were untraced. Since then 8 of the 15 have been traced and 2 of these were found alive and well. This gives 29 patients surviving from five to ten years after treat-

ment—23.9 per cent. The original grouping of these cases was according to the Schmitz classification. Recently they have been regrouped according to the League of Nations classification to facilitate comparison with series so classified, and this shows as follows: 3 cases in Stage I (all survived); 11 cases in Stage II (5 survived); 97 cases in Stage III (21 survived); and 10 cases in Stage IV (none survived). Two of the Stage I cases were subjected to operation, one receiving and the other not receiving subsequent x-ray treatment. One very early Stage II case received operation in addition to radium and x-ray. From present knowledge I feel certain that operation added nothing to the chance of cure in these cases and that they would have survived the same with our regular irradiation treatment alone, as did the other Stage I patient who received only that. For these reasons it seems only fair to count the series as a unit in estimating the results of our regular irradiation course. It certainly would not be fair to count out these most favorable cases in estimating the effectiveness of the method.

TABLE I. COMPARISON OF SERIES BY GENERAL PERCENTAGE OF FIVE-YEAR CURES

SERIES	NUMBER OF CASES	FIVE-YEAR CURES	PERCENTAGE
Regaud	317	107	33
Healy	1,574	352	22
Ward	343	85	24
Burnam	349	70	20
Barnes Hospital	121	29	23

The results attained by the methods employed in the various series mentioned are shown in Table I. For convenience and clearness decimals are omitted. The high percentage of cures attained by Regaud would indicate that the method he uses is greatly superior to the others—provided this great difference is due to the method employed. We must bear in mind, however, that there is another factor having great influence on the total percentage of cures in a series, namely the relative proportion of early and late cases. With the same efficiency of treatment, a disproportionate number of early cases in a series will send the general percentage of cures up or a disproportionate number of late cases will send it down.

It is clear that when comparing results in different series they should be compared class by class—early cases to early cases and late cases to late cases. That is the only way we can ascertain the real efficacy of the different methods.

TABLE II. COMPARISON BY CLASSES

	STAGES I AND II	FIVE-YEAR CURES	PER-CENTAGE	STAGES III AND IV	FIVE-YEAR CURES	PER-CENTAGE
Regaud	118 (37%)	60	51	199 (63%)	47	23
Barnes Hospital	14 (12%)	8	57	107 (88%)	21	19

Table II shows such a comparison of the Regaud series with the Barnes Hospital series. The comparison of these two series class by class shows that there is practically no difference in the results attained

by the two methods of treatment. In the early cases the Barnes Hospital method is higher by six points and in the late cases the Regaud method is higher by four points. So the marked difference between 33 per cent of cures and 23 per cent of cures is not due to the method employed, but to the larger proportion of early cases attracted to the Radium Institute of Paris.

This marked influence of a large proportion of first- and second-stage cases on the general percentage of cures is shown also in the analysis of Ward's series. It was seen in Table I that this series has a general cure percentage of 24, the highest in the American series. Now this is the series in which occurred the nearly 50 per cent of reradiations, previously referred to and presumably due to insufficient primary radiation, and yet the series shows the highest general rate of cure. However, when the results are compared class by class, there is a different picture.

TABLE III. ANALYSIS OF WARD'S RESULTS

	STAGES I AND II	FIVE-YEAR CURES	PERCENTAGE	STAGES III AND IV	FIVE-YEAR CURES	PERCENTAGE
Ward	208 (60%)	71	34	135 (40%)	14	10
Combination (Healy, Burnam, Barnes Hospital)	466 (23%)	219	47	1,578 (77%)	232	14

Table III presents such an analysis of this series class by class and a comparison with the other American series (Healy, Burnam, Barnes Hospital). This shows clearly that the high general rate of cure (24 per cent) is due to the large proportion of first- and second-stage cases and not to the method of treatment. In fact, comparison of results class by class shows that the method employed gave poorer results in both the early and the late classes—as to be expected from the large percentage of reradiations for recurrence at the vaginal vault.

A careful consideration of statistics so far available, on the basis of five-year cures in similar classes of cases, therefore, shows the following in regard to the general methods of radium treatment:

1. The method of giving a moderate dose and then watching and reradiating if local recurrence appears, may be definitely ruled out. Ward's work at the Woman's Hospital of New York is the best representative of this method and, as already stated, he had a very large percentage of local recurrences requiring reradiation, and his percentage of cures is lower in both groups of cases.

Keene of Philadelphia, who used this method up to about two years ago, states in his published report[8] that he was so dissatisfied with results that he had entirely reorganized his plan of attack.

I am criticizing these various methods in a purely impersonal way. I am interested only in determining, as far as possible, what is best from

the standpoint of curing the patient. Each physician mentioned is a splendid worker—conscientious, industrious, and eager to employ promptly every real advance. We are all working to give our cancer patients the very best service, and if any method was employed that fell short, it was simply an error of judgment that any of us might have made, or may make, in connection with these complicated problems. Perhaps there is some error in my own calculations and conclusions. If so, I shall be glad to have it pointed out.

2. The second conclusion is that the choice of radium methods has narrowed down to full dosage near the beginning of treatment—either in a single concentrated dose or spread out over about a week.

TABLE IV. RADIUM METHODS

	AMOUNT	TIME	DOSE	SCREENING
Regaud	60 mg.	5 to 7 days continuously	7,000	1.5 mm. platinum
Healy	100 mg.	5 to 7 days interruptedly	7,000	0.8 mm. platinum
Burnam	1-3 gm.	2 to 3 hours	4,500	0.8 mm. platinum
Barnes Hospital	100 mg.	1 to 2 days	5,000	0.8 mm. platinum

Table IV shows the variations in the spread-out treatment method and in the concentrated treatment method. The dose figures indicate the milligram-hour maximum dosage. Of course, in many patients the conditions are such that the radium dosage must be considerably reduced—more dependence being then placed on the supplementary deep x-ray therapy, which is used in all cases.

Regaud employs continuous application for from five to seven days of from 50 to 60 mg. of radium, with screening equal to 1.5 mm. of platinum. Healy employs interrupted treatments over a period of from five to seven days, using a moderate amount of radium and also at times emanation (radon). The principal difference between these two variations of the spread-out method is that Regaud uses a small amount of radium continuously for from five to seven days, while Healy uses a somewhat larger amount interruptedly for the same period and the same dosage.

Burnam uses a very large quantity of radium (from 1 to 3 gm.) for cervical application leaving it in for from two to three hours for the maximum dosage of about 4,500 mg. hr. In the Barnes Hospital series we used about 100 mg. of radium applied continuously for approximately two days, for the concentrated maximum dose of 5,000 mg. hr.

Taking up now the results attained by the spread-out method and the concentrated method, comparison has already been made, in Table II, between the Regaud series and the Barnes Hospital series. Table V shows comparison of results attained by American representatives of the two methods. This comparison class by class shows no superiority of the spread-out method over the concentrated method. In fact, the

latter is twelve points higher in the early class and only two points lower in the late class, while comparison with the Barnes Hospital series alone shows that the concentrated method has a somewhat higher cure rate in both the early and late classes.

TABLE V. COMPARING SPREAD-OUT TREATMENT WITH CONCENTRATED TREATMENT IN THIS COUNTRY

	STAGES I AND II	FIVE-YEAR CURES	PERCENTAGE	STAGES III AND IV	FIVE-YEAR CURES	PERCENTAGE
Healy	387	174	45	1,187	178	15
Burnam and Barnes Hospital	79	45	57	391	54	13
Barnes Hospital alone	14	8	57	107	21	19

Incidentally, I desired to know whether the use of very large amounts of radium would show results superior to those obtained with moderate amounts. With the large amount of radium available for many years at the Kelly Hospital, Burnam has been able to conduct valuable experiments in this direction, both with radium element and with radium emanation (radon).

TABLE VI. COMPARING RESULTS FROM 3,000 MG. AND 100 MG. OF RADIUM

	STAGES I AND II	FIVE-YEAR CURES	PERCENTAGE	STAGES III AND IV	FIVE-YEAR CURES	PERCENTAGE
Burnam	65	37	57	284	33	11
Barnes Hospital	14	8	57	107	21	19

Table VI shows a comparison of the results obtained with a very large amount of radium and with a moderate amount, each being used by the concentrated-dose method. This comparison shows no superiority of results from the very large amount. In the early cases results are identical, and in the late cases the Barnes Hospital series shows a slightly higher percentage of cures. Of course, we may have been especially fortunate with this series, and a larger one may show different results in this respect. Also, in this connection, the efficacy of the accompanying x-ray treatment must be taken into consideration, and I feel that our good results are due partly to the splendid x-ray service under the direction of Dr. Sherwood Moore. This has now expanded into the Mallinckrodt Institute of Radiology, occupying its own eight-story building in the Washington University clinical group and furnishing service to the Barnes Hospital and other departments of the Medical School.

Looking to the future, there are two improvements in treatment that we seek: first, more extensive and certain devitalization of the outlying cancer cells; and second, less inflammatory stir-up and less tissue destruction at the site of radium application. How to secure these improvements and thus cure a still greater percentage of patients is the live problem of today.

It is possible that the advance will come through further developments along the line of the spread-out radium application adjusted to stages of cancer cell division, but so far statistics give no hope in that direction. Personally, I feel that the best hope of securing these desired improvements lies in the increasing efficiency of deep x-ray therapy. As this deep therapy efficiency increases we may be able to substitute x-ray concentration on the cervix region for a part of the radium dose. That would permit a smaller, less irritating dose of radium and still maintain the full cancer dosage at the vaginal vault.

CONCLUSIONS

1. In regard to general radium methods, the choice has narrowed down to full dosage near the beginning of treatment. The method of giving a moderate dose and then waiting to see if more is needed, has been definitely ruled out—both by the rational strategy of radium attack on cancer cells (full dosage before radium resistance develops) and by extensive experience with the method showing poorer results in both the early and late cases.

2. Of the two methods of giving full dosage near the beginning of treatment—the concentrated dose and the spread-out dose—statistical analysis of representative series shows no superiority in results of the latter over the former. In fact, as far as American work is concerned, the concentrated dose shows the better results. This answers definitely the question which started the inquiry, namely, "Should we change from our concentrated dose to the spread-out dosage?"

3. For attaining the two important future objectives—more certain devitalization of outlying cancer cells and less destructive reaction at the site of the radium application—the best hope seems to lie in the increasing efficiency of deep x-ray, which may permit the substitution of x-ray concentration on the cervix for a part of the radium dose.

4. In comparing the results of different methods of treatment, the comparison should be made class to class—early cases to early cases and late cases to late cases.

5. The League of Nations classification should be used universally. A uniform international classification of cases is imperative for comparison of results of various methods of treatment. The League of Nations classification is satisfactory; it is already in rather general use and is the only classification likely to come into universal use.

In the case of each patient, the evidences of the extent of involvement should be worked out sufficiently to permit accurate assignment to class. Accuracy is enhanced by deciding definitely as to the class at the time of examination and then recording the decision. This obviates the difficulty encountered when trying later to classify a borderline case with some needed detail missing.

6. An incidental revelation of this statistical study is that certain institutions have been able to educate their clientele to such an extent as to obtain a large percentage of first- and second-stage cases, as evidenced by Regaud's series showing 37 per cent and Ward's series showing 60 per cent, in contrast to the 23 per cent average of other series. This is a most encouraging fact, and it contradicts the assertion sometimes made that cancer educational efforts produce no tangible results. This splendid showing in regard to the percentage of early cases by the Radium Institute of Paris and by the Woman's Hospital of New York, constitutes a pointed lesson to the rest of us to get busy in carrying out an effective educational program among our own hospital patients and their friends.

REFERENCES

(1) *Lacassagne:* Brit. M. J. **2:** 912, 1932. (2) *Ward, G. G.:* Surg. Gynec. Obst. **56:** (No. 2A) 434, 1933. (3) *Healy:* J. A. M. A. **97:** 1680, 1931. (4) *Idem:* Ann. Surg. **93:** 451, 1931. (5) *Burnam:* Surg. Gynec. Obst. **56:** (No. 2A) 427, 1933. (6) *Crossen:* AM. J. OBST. & GYNEC. **22:** 559, 1931; and *Newell:* AM. J. OBST. & GYNEC. **24:** 167, 1932. (7) *Ward:* AM. J. OBST. & GYNEC. **22:** 543, 1931. (8) *Keene:* Surg. Gynec. Obst. **56:** (No. 2A) 416, 1933.

EXPERIENCE WITH RADIATION THERAPY IN CANCER OF THE CERVIX*

WILLIAM P. HEALY, M.D., NEW YORK, N. Y.

CANCER of the cervix not only is a chronic disease, but it is a deadly disease. Rarely, if ever, has a spontaneous cure been observed in a patient suffering from cancer of the cervix. It is a disease that becomes progressively worse and, untreated, terminates the patient's life in from two to three years.

Cancer is a disease that establishes itself, insidiously, in the cervix and can progress to an advanced stage quite easily before being recognized, since the cervix is a silent area and has no active function to perform, interference with which by the growing cancer might attract early attention.

The records of the Memorial Hospital of New York show that we have had under observation and treatment from 1916 to 1933 inclusive about 3,000 cases of cancer of the cervix. Approximately 2,500 of these cases were classified as primary and the remainder as secondary or recurrent.

In reviewing this large series of cases one obtains certain impressions. Etiologically, for instance, nothing new is identified. All but 4 or 5 per cent of the patients have given birth to children, possibly bearing out a relationship between cervical injury in labor and the

*Read at meeting of the Obstetrical Society of Philadelphia, February 1, 1934.

subsequent onset of cancer in the damaged tissues. A fair number of the cases have a family history of cancer in one part of the body or another. Schafer recently studied the question of heredity in 100 cases of carcinoma of the cervix under observation in Stoeckel's clinic and states that a history of carcinoma was present in 22 per cent. In most cases the history indicated involvement of a sex organ. Differences in racial predisposition are recognized but not explained. We seem to see an unduly large proportion of Italian patients suffering from cancer of the cervix and relatively few Jewish patients, although both races are known to be very fertile.

Infection alone as indicated by an antecedent history of endocervicitis of neisserian origin or of adnexal inflammation seems not to be a predisposing factor. At any rate we have not been able to identify it as such.

Despite the fact that the average age incidence is between the forty-fifth and fiftieth years we are quite certain that the number of patients under thirty-five years of age appearing at the Memorial Hospital for treatment of cervical cancer is on the increase. These younger patients often have not conceived at all and rarely give a history of unusual multiparity.

Diagnosis, unfortunately, seldom offers any problem in our cases since the disease is usually so well established in 95 per cent of the patients that a clinical diagnosis, without biopsy, may be made readily. However, biopsies are done on all cases routinely for the twofold purpose of exact diagnosis and histologic grading.

We are encouraged to believe that earlier diagnosis may be made more frequently in the future as more and more patients with nonmalignant cervical lesions are being referred to the clinic by their physicians who regard the lesions as possibly malignant. This careful scrutiny and cautious attitude by the attending physician toward abnormal cervices should certainly lead to more prompt recognition of the disease when it is present. On the other hand proper therapeutic measures directed toward the cure of benign cervical lesions may also be expected to reduce the incidence of cervical cancer.

From the diagnostic standpoint the Schiller iodine test may be helpful by directing our attention to suspicious areas on the nonulcerated surface of the portio vaginalis of the cervix. Lugol's solution is used for the test and it depends upon the presence of glycogen granules in the surface layer of the normal epithelium of the portio and the absence of glycogen in carcinoma cells even in the initial stage of disease. The glycogen content also seems to disappear in the keratosis associated with leucoplakia.

The test is simple enough: one swabs the suspected area or the entire portio with the solution and then promptly mops off the excess. Immediate inspection is made with a good light and if one or more well-

demarcated unstained areas are visible further investigation is indicated. The unstained area suggests leucoplakia or early carcinoma without ulceration.

It is impossible to make an exact diagnosis without biopsy on the suspected area of white surface epithelium and a careful histologic study by a competent tissue pathologist.

As Schiller says, the object of the iodine application is to call attention to suspicious spots. It cannot do more. A negative result with the iodine test does not rule out the possibility of carcinoma in the deeper portions of the cervix not involving the surface epithelium.

The iodine test is not applicable to a suspicious ulceration or erosion, as it is useful only in the presence of squamous epithelium.

The iodine test has not been helpful to us thus far as all cervix cases referred to the Memorial Hospital present ulcerated lesions. However, I believe it may be used to advantage in general gynecologic clinics and from time to time through its use otherwise unsuspected cases of cervix carcinoma may be discovered early in the disease before ulceration has occurred and when the chance of obtaining a permanent cure of the disease is excellent.

Pregnancy coincident with cancer of the cervix has occurred only three times. Two of the patients died in less than eighteen months after treatment, the third is now under treatment. We have had three patients, all under thirty years of age, in whom the disease seemed to have appeared during the puerperium. In each instance the disease was well established clinically when treatment was started but completely disappeared under radiation therapy, and the patients are still living, one six years, another two years, and the third was treated only four months ago.

Arneson in a recent review of our cases from January, 1920, to July, 1933, with regard to the occurrence of carcinoma in the cervical stump after subtotal hysterectomy found it in 2.6 per cent. No case was included in his series in which the disease appeared in less than three years following the subtotal hysterectomy in order to avoid possibility of error in the original diagnosis.

Forty-eight per cent of the lesions occurred from three to ten years and 37 per cent from ten to twenty years after the hysterectomy. Histologically 94 per cent of the lesions were squamous epidermoid in type and 6 per cent were glandular or adenocarcinoma. As the disease in the adenocarcinoma cases did not appear in less than six years after the operation it would seem reasonable to assume that they were instances of primary cervical cancer.

The prognosis is more grave in patients with carcinoma in a cervical stump. The total five-year salvage in our series of 64 treated cases as reported by Arneson was 14 per cent as against 22.6 per cent in all cervix cases treated at the Memorial Hospital.

Dean, of the Department of Urology, estimates that 2.1 per cent of our cases of cervix cancer treated by irradiation will develop post-

radiation trophic bladder lesions one year or more after treatment. The lesions often are ulcerative and are always located in the posterior third of the bladder base. They respond as a rule to local treatment consisting of boric acid or phosphoric acid irrigations, instillation of solutions of argyrol when there is much pain or mercurochrome if pain is not severe. Treatment may have to be carried on over a period of months before the ulcer is entirely healed.

Does radiation therapy increase the incidence of fistulas associated with cervical cancer? Smith in a recent paper dealing with this question reviewed all of our cases of cancer of the cervix, either primary or recurrent, observed and treated by irradiation during the years 1916 to 1932 inclusive, a total of 2,852 cases.

Ninety-four fistulas occurred, an incidence of 3.2 per cent. This could be subdivided into 2.5 per cent occurring in the cases of primary cervical cancer and 6.4 per cent in the recurrent cases.

In the primary early cases of cervical cancer the incidence was 1 to 72.5; in the advanced primary group 1 to 36.4. The frequency was 1 to 16 in the recurrent group and the cervical stump group.

These figures would seem to bear out the assumption that the absence of the uterus increases the chance of fistula if radiation therapy becomes necessary.

Smith's study also verifies our impression that advanced disease plus infection markedly predisposes to fistula formation, especially if the lesion is first treated by surface or interstitial application of radium. Whereas if the necrotic, infected cancer field receives preliminary roentgen ray therapy and the radium treatment is delayed from one to two weeks, the infection will usually have diminished and the response to radium therapy will be more satisfactory with less risk of fistulas.

Our experience suggests that interstitial radiation if used at the time of the primary treatment increases the tendency to fistula formation.

Another point is the danger of retreatments; only 11.4 per cent of our cervix cases have required retreatments, whereas 67.6 per cent of the fistula cases received retreatments. In our series rectovaginal fistula was more common than vesicovaginal or than combined rectovaginal and vesicovaginal fistulas.

If pyometra of any extent is present when the patient is first seen it will delay the application of radium. A rubber catheter is placed in the uterine cavity for drainage and to permit daily cleansing of the cavity with weak antiseptic solutions. In the meantime deep roentgen ray therapy is carried out, usually one pelvic cycle of 700 or 750 R to each field. If the pyometra subsides, radium is applied either in full or divided doses. Some patients never improve sufficiently to per-

mit radium to be used. Under those conditions if hysterectomy is at all feasible, it should be done as a palliative measure. When pyometra develops as a late or postradiation lesion, it is best treated by hysterectomy.

In 1929 we instituted the routine use of the deep roentgen ray pelvic cycle before applying radium in our advanced cases of cervix cancer. This procedure was planned to clean up the primary lesion and usually resulted in marked improvement. The soft, infected, more or less necrotic surface would disappear and leave a more firm, red, healthy-looking surface to which radium could be applied from one to two weeks after the roentgen ray cycle with less risk of slough, infection, and cellulitis.

Incidentally, one of the worst things that can happen to a patient with advanced cancer of the cervix is to have a combination of radiation slough and infection.

It is five years since this plan was established and I am glad to say we are convinced from our observation of these cases that it is superior to our previous plan of radium first and roentgen ray second. There have been less constitutional reactions and fewer local complications have followed the present method.

A year or more ago in studying our own end-results as well as those of well-known clinics throughout the world it was evident that we were all obtaining about the same percentage of total salvage or five-year end-results, usually from 20 to 25 per cent, and that the peak had been reached with the methods of treatment then in use.

It was also evident that we were achieving rather uniform success in curing the primary disease of the cervix, but the patients were dying from continued growth of uncontrolled parametrial disease and its later extension into the retroperitoneal lymphatics and other structures.

One can readily understand that radium applied in the vaginal canal against the cervix or in the cervical or uterine canals cannot be effective in destroying cancer tissues or cancer cells more than one and one-half inches away from the point of application of the radium.

It would seem urgent and imperative for us to develop if possible a safe and efficient method of taking care of the parametrial metastases. With this in mind we have for the past year been employing a more intensive plan of external roentgen radiation for the parametrium.

The plan is based on increasing the skin dosage, in order to obtain a greater intensity of effective radiation in the deep pelvic tissues through the use of multiple small dosages of roentgen ray given daily, until a much greater sum total of R units has been given to each field than could possibly be given in a single treatment without very severe skin and tissue damage. Also the target skin distance was increased so as to give a greater percentage depth dose in the parametrium.

Under the old plan each of the four pelvic fields, two anterior and two posterior, received a total of from 700 to 750 R units and only one treatment was given to each field. The treatments were given daily or on alternate days. Under the multiple dose plan, the pelvis is divided into a right and a left half and each half into an anterior and a posterior field. The two fields in one-half of the pelvis are treated one day, 200 R to each field at 70 cm. and the two fields in the other half the following day. In this way the patient received daily treatments to one-half of the pelvis, 200 R at each exposure until each field has received 1,000 R, then the dosage for each exposure is increased to 300 R and treatments are continued daily as before, until an additional 1,500 R have been given to each of the four pelvic fields, making a final total of 2,500 R to each quadrant, as against the former total of 750 R.

It is estimated that under this plan the parametrial structures 10 cm. below the skin surface receive the equivalent of about two-thirds the total skin dose. About twenty-three or twenty-four days are required to finish the treatment.

The patients as a rule stand the treatments well, unless they have to travel a long distance daily to the hospital; if so they should be hospitalized during the treatment.

The skin reactions have been marked in 10 per cent, amounting to desquamation and raw surface especially in the groins. In 80 per cent the skin reaction has been moderate, and in 10 per cent there has been little or no reaction. The bladder and rectal symptoms have not been annoying. Radium in full dose has been applied to the primary lesion at the end of the roentgen ray treatments.

Since one-half of the cervix was included in the roentgen ray treatments given each day, we were fortunate in being able to follow clinically by visual inspection and histologically by repeated biopsies on the cervix the response or behavior of the primary lesion during this treatment. Similar changes might be expected in cancer foci in the parametria.

It was interesting to note that there was a steady response on the part of the primary lesion both clinically and histologically in practically every instance while the treatment was carried on. This response was so marked that in many instances the diseased cervix healed over superficially while under roentgen ray treatment and before radium was applied.

It is important to emphasize that radiation given in this manner within the limits of tolerance of normal structures such as skin, fat, intestines, bladder, rectum, nevertheless caused a marked regression in the cancer indicating again the difference in radiation sensitivity of normal tissues and cancer cells.

We believe, from our experience with the above method, that some plan similar to this one can be devised which will materially raise the percentage of five-year cures in the advanced group of cervix cancers.

121 East Sixtieth Street

DISCUSSION

DR. BROOKE M. ANSPACH.—It is apparent that most cancer patients come too late. The only way to keep track of cancer patients is to have them return every month. In our Cancer Clinic at the Jefferson Hospital we have kept in touch with every patient since 1928. We classify our cases histologically, at the suggestion of Dr. Baxter L. Crawford, as of high, intermediate and low-grade malignancy. Clinically, we use the widely known classification of Schmitz. We use a large dose of radium at the outset, for a time as high as 4,800 mg. hours. At present we have standardized the dose at 3,600 mg. hours. We have given up operation for carcinoma of the cervix because we believe radiation gives equally good results and with a small mortality. Relative to the latter, in our first series of 104 cases, there was one death; in 98 cases since that time, there have been three deaths, a total mortality in the 202 cases of 3 per cent.

A distinction may be drawn between the so-called five-year cures and the present-day cures, since some of the patients apparently free of cancer at the end of five years have a recurrence later. In a five-year classification we have 5 more patients who apparently were cancer-free at the expiration of that time, so that our five-year absolute percentage is 21.9. Of the patients treated (104) our present-day curability, which we may speak of as relative, is 19.2 per cent and our five-year relative curability is 24 per cent.

DeCourcy, J. L.: Resection of the Presacral Nerve for Dysmenorrhoea, Am. J. Surg. 23: 408, 1934.

The author's surgical technic is as follows: When the promontory of the sacrum is uncovered it is possible to see the fibers of the presacral nerve crossing the left iliac vein. The posterior parietal peritoneum is opened by an incision bisecting the pelvic triangle which lies between the iliac vessels. All the fibers in this triangle are picked up upon a ligature carrier, and are entirely stripped away, care being exercised not to omit any fiber however insignificant. The peritoneum is then closed over this resection.

The author strongly recommends this procedure for the relief of obstinate cases of dysmenorrhea which have proved resistant to ordinary measures. Good judgment in the selection of suitable cases is a prime requisite. This procedure offers a means of aiding a large class of women who must otherwise suffer a monthly martyrdom and be compelled to drag out the greater part of their time in partial disability with a general lowering of physical and mental efficiency.

J. Thornwell Witherspoon.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES

MILTON E. KAHN, B.S., M.D., F.A.C.S., BUFFALO, N. Y., AND SAMUEL NORRIS, M.D., TORONTO, CANADA

(From the Departments of Gynecology and Pathology of the Buffalo General Hospital and the University of Buffalo School of Medicine)

SINCE Orthmann's[1] description of primary carcinoma of the fallopian tube in 1888, additional reports have brought the total cases to 270. Of this number Johnson and Miller[2] in 1931 reviewed 250 cases and added one of their own. Various investigators contributed the remainder. During the past decade, the incidence of the disease seems on the increase. This may be more apparent than real and is probably due to a more highly "carcinoma-minded" profession and laity plus a more general microscopic examination of excised surgical specimens. It is our purpose to present four additional cases of primary carcinoma of the oviduct, including the youngest cases yet on record.

CASE 1.—Mrs. R. G., white, aged fifty-five, was admitted to the hospital complaining of profuse, brownish vaginal discharge. She had never been pregnant. Menstruation had always been irregular, occurring from every two to four months. The menopause at forty-eight was uneventful. Her past history revealed repeated gastrointestinal upsets which she described as "biliousness" and an attack of influenza eight months previous to admission. Her present illness began six months before her entrance to the hospital when she noted a thin brown vaginal discharge. This came on suddenly, was profuse in amount and persisted until admission. Constant protection was necessary, requiring up to fourteen vaginal pads daily. Frank vaginal bleeding was not observed. For the past month she had noticed an occasional bloody discharge from the umbilicus. She had not complained of abdominal pain. Her weight had been constant.

Physical examination of the head, neck, and chest was normal. In the left lower quadrant of the abdomen was a mass the size of a hen's egg, cystic, fixed, and tender to pressure. There was no objective evidence of peritoneal fluid. Examination of the umbilicus revealed nothing abnormal. On vaginal examination, a profuse thin, brownish discharge was noted. The uterus was normal in size and position. Arising from the left side of the pelvis and extending into the culdesac was an orange-sized adnexal mass which was fixed and tender. Her temperature and pulse were normal.

Blood count showed erythrocytes 4,200,000, hemoglobin 70 per cent (Sahli) and leucocytes 8,250. Urinalysis revealed a moderate amount of albumin.

A preoperative diagnosis of a left hydrosalpinx was made. On opening the abdomen a large, adherent, distended tube was seen arising from the left side and extending behind the uterus. In palpating this tube there was a peculiar consistency giving the impression of solid and fluid contents intermixed. On the right side, the tube and ovary were normal in size but bound firmly by old adhesions. They were not disturbed. The uterus appeared normal. A left salpingectomy and ovariectomy were done. Convalescence was uneventful.

On gross examination, the tube was dilated throughout its length, more particularly its outer third. The fimbriated extremity was sealed. On section a quantity of brown, serous fluid escaped. Arising from the mucosa and filling the lumen were numerous papillomatous tumor masses. A microscopic diagnosis of primary adenocarcinoma papillomatosum of the fallopian tube was made. The ovary contained scattered follicular cysts.

Three months after the operation, the patient was readmitted because of a painful umbilical hernia. On exploration the hernial sac was found to contain omentum which was studded with metastatic tumor, microscopically, papillary adenocarcinoma. Following this operation the patient moved to a nearby city where death occurred two months later.

CASE 2.—Mrs. M. K., white, aged fifty-three, was admitted to the hospital complaining of a bloody vaginal discharge, lower abdominal pain and backache. She had had a normal labor and puerperium twenty-one years before. There were no abor-

Fig. 1.—Bilateral tubal carcinoma. Uterus distended with slightly bloody fluid similar to that which distended the one tube. The cavity of the uterus was smooth and everywhere free of carcinoma. (Semidiagrammatic.)

tions or miscarriages. Menstruation had always been normal, the menopause occurring at forty-nine. Four months before admission, she began to have a bloody vaginal discharge which necessitated the constant wearing of a vaginal pad. This discharge continued until her entrance into the hospital and was associated with bilateral lower abdominal pain and sacral backache. Her weight had been constant.

Examination elicited a slight generalized tenderness across the lower abdomen. The uterus was in normal position and for a woman of her age, slightly enlarged. The adnexa were not palpable or tender. The cervix appeared normal. No abnormalities were found in the blood or urine.

The preoperative diagnosis was uncertain. Atrophy of the endometrium or corpus carcinoma were considered. On curettage, no endometrium was obtained. The cervix appeared normal. An intrauterine radium application of 400 mg. hours was given and the patient discharged on her fourth postoperative day.

Three weeks later the bloody, vaginal discharge recurred. Examination at this time revealed a plum-sized, tender swelling of the left adnexa. Six weeks later

vaginal bleeding was still present and the adnexal mass had definitely enlarged. Exploratory laparotomy was performed.

At operation, the left tube was enlarged, cystic and densely adherent in the culdesac. From its uterine end, the tube gradually increased in diameter, its distal half attaining the size of a large peach. Its fimbriated extremity was sealed. In freeing the tube, it ruptured and a large quantity of serosanguineous fluid escaped. The corresponding ovary appeared cystic. On the right side the tube was moderately thickened and its fimbriated end closed. It was firmly adherent to the ovary. The uterus appeared normal. Bilateral salpingectomy and oophorectomy and supravaginal hysterectomy were done. On cutting across the cervix, a quantity of brownish serous fluid escaped from the cavity of the uterus.

Upon section (Fig. 1) the proximal half of the left tube was found filled with a spongy, papillary growth. Its lumen contained a quantity of brownish serous fluid.

Fig. 2.—Section of left tube showing epithelial, papillary proliferations filling the lumen (low power).

The proximal half of the right tube showed a similar growth. Both ovaries appeared moderately cystic. The uterus showed nothing of interest grossly.

Microscopically (Fig. 2), the lumen of the larger tube (left) showed papillary projections formed of epithelial proliferations. These contained many irregular glands which extended slightly into the muscularis but did not excessively invade the wall of the organ. Strands and masses of cells and actual glands were found invading the fibrous stroma of the mucosa and submucosa and to a slight extent, the muscularis. There was a marked round cell infiltration particularly along the advancing borders of the tumor and also in the deeper layers of the tube. Some young fibrosis was noted. Similar findings were present in sections of the tumor of the right tube. The uterus showed a marked atrophy of the endometrium. The ovaries contained a few apparently old graafian follicle cysts. The pathologic diagnosis was bilateral, primary adenocarcinoma of the fallopian tubes.

Postoperative irradiation was given. During the next eight months the patient improved greatly and gained twenty pounds in weight. Pelvic examination revealed

no evidence of recurrence. However, four months later she returned with a walnut-sized mass at the left angle of the abdominal incision. Five months later the mass had enlarged to the size of an egg. It seemed movable on the underlying fascia.

At operation, a well-encapsulated cystic tumor was found lying above the fascia. It was dark in color and semifluctuant. In dissecting the sac free, it ruptured and papillomatous tissue escaped. There was extensive hemorrhage into the wall of the sac and into the surrounding fatty tissue. The pathologic report was metastatic papillary carcinoma with marked inflammatory reaction (Fig. 3).

Therapeutic x-ray was continued and when last seen in September, 1933 (three years and eight months after laparotomy), the patient was apparently well. Vaginal bleeding or discharge had not reappeared, and there was no palpable evidence of recurrence either in the abdominal wall or in the pelvis.

CASE 3.—Mrs. M. W., white, aged eighteen, was admitted to the hospital on Sept. 10, 1930, complaining of pain across the lower abdomen, irregular vaginal bleeding,

Fig. 3.

Fig. 4.

Fig. 3.—Metastatic, papillary carcinoma at the site of the abdominal incision (medium power).

Fig. 4.—Section of right tube showing the glandular and papillary formations in the wall (microsummar).

and a loss of forty pounds in weight. She had never been pregnant. Menstruation had begun at twelve, had been painless and regular every four weeks and lasted from two to three days. Her past history revealed a multiple generalized furunculosis in 1924, and diphtheria in 1926. In 1927 at the age of fifteen, she had been treated in the Out-Patient Department for a right Bartholinitis, the etiology of which was not determined. Eight months previous to her admission, she noticed for the first time prolonged, profuse menstruation marked by severe, bilateral lower abdominal pain. The next month she was married. Subsequently her periods became irregular with somewhat increased flow. For five months before admission there was a daily vaginal "spotting" which was frankly bloody in appearance. Abdominal pain was alternately dull and sharp and persisted to admission. During the last month it was unusually severe. Since the onset of her present illness she had lost forty pounds in weight.

On examination, the patient appeared older than the stated age of eighteen years. Her skin was of a decided yellowish tinge. There was tenderness on moderate

pressure over both tuboovarian regions. Muscle spasm was absent. On vaginal examination, there was slight bleeding observed. The urethra was free of discharge. The vulvovaginal glands could not be palpated. The uterus was anteverted, small, and movable without pain. Both adnexa were enlarged, thickened, tender, and fixed. The cervix appeared normal. Because of the bleeding, smears were not taken. The temperature and pulse rate were normal.

Blood examination showed: erythrocytes 3,950,000, hemoglobin 75 per cent, leucocytes 10,200, and differential count normal. The urine showed a trace of albumin.

At operation, the peritoneal cavity contained approximately 200 c.c. of a straw colored, slightly blood-tinged fluid. The omentum was adherent to the right uterine cornu and was studded with many small, yellow, tubercle-like lesions. The uterus appeared normal except for a few fine adhesions to its posterior surface. On the right side, the adnexa were firmly adherent to the floor of the pelvis. Separation

Fig. 5.

Fig. 6.

Fig. 5.—Section of left tube which shows similar glandular structures in the wall (microsummar).

Fig. 6.—Section through a glandular unit in the wall as shown in Fig. 5 (medium power).

of these adhesions was accompanied by profuse bleeding. The tube was enlarged, very friable and on the surface of its ampullar portion was a caseous-appearing lesion about one centimeter in diameter, resembling tuberculosis. The adnexa of the left side presented a similar picture. The fimbriated ends of both tubes were closed. Excepting for surface adhesions, both ovaries appeared normal. Bilateral salpingectomy was done and a piece of omentum removed for pathologic examination.

The pathologic findings were as follows: Both tubes were enlarged and thickened, particularly in their outer two-thirds. Their serous coats were markedly injected. On the mesosalpinx of the right tube were yellowish nodules suggesting tuberculosis. The tag of omentum contained many wheat grain-sized lesions.

Microscopically, the right tube (Fig. 4) showed a very marked chronic inflammation. There were many leucocytes and plasma cells present throughout, particularly in the mucosa. In the muscular and subserosal layers were many round and eosinophile cells. In all layers there were glandular and papillary formations.

These were more numerous in the serosa but were also to be found here and there in the lymph vessels. The left tube (Figs. 5 and 6) showed the same glandular formations and inflammatory processes in all layers. Particularly marked were the metastases in the lymph vessels of the serosa. The piece of omentum (Fig. 7) showed typical epithelial papillary groupings. The diagnosis was bilateral papillary carcinoma with omental metastases.

Two months after operation the patient was readmitted complaining of irregular vaginal bleeding, lower abdominal pain, and dysuria. These symptoms had been present for four weeks. There had been no further loss of weight. On examination, the uterus was in anterior position, slightly enlarged and tender. On the left side was a tender, fixed mass the size of a hen's egg. The right fornix was free.

The uterus was curetted but very little material was obtained. An intrauterine application of 600 mg. hours of radium was given. Microscopically, the curettings showed slight glandular hyperplasia of the endometrium. No evidence of malignancy was seen.

The patient was again admitted Feb. 19, 1931, five months after the first operation. She complained of nausea, vomiting and diarrhea of two weeks' duration.

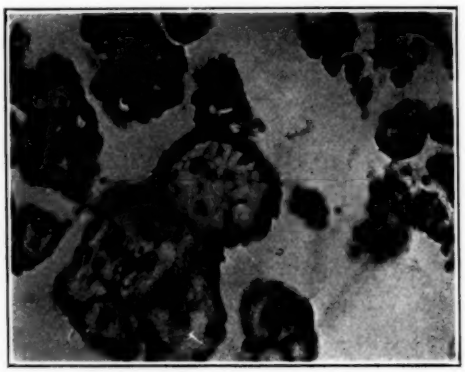


Fig. 7.—Omental metastases from papillary carcinoma of the tubes (high power).

The stools were frequent, but not bloody. Pelvic findings were essentially unchanged. After a week in bed her symptoms cleared spontaneously and she was sent home.

On her fourth admission four months later, she complained of lower abdominal pain and bloody vaginal discharge. The discharge had been present daily for the past month. The uterus was in normal position and fairly movable. Behind the uterus and extending to the left was a tender enlargement which lacked the firmness of carcinoma and which gave the impression of a cystic ovary. No palpable evidence of a malignant recurrence could be found.

Curettage was again performed. Very little material was obtained. Fifty milligrams of radium in a brass capsule was inserted into the fundus for twenty-four hours. Microscopically, the endometrium showed a slight glandular hyperplasia without signs of malignancy.

Subsequently for two years and three months the patient was followed in the Out-Patient Department. During this time she was treated with x-ray and pelvic diathermy. When last seen on Sept. 29, 1933, three years after laparotomy, she had gained twenty pounds in weight. Menstruation had been irregular, occurring every one to three months with scanty flow. There had been no further vaginal discharge. Her only complaint was an inconstant lower abdominal pain.

The uterus was normal in position, size, and mobility. The left ovary was the size of a plum, cystic, and much less tender than on previous examinations. No evidence of carcinoma was found.

CASE 4.—Mrs. J. H., white, aged eighteen, was admitted to the hospital on Oct. 6, 1932, complaining of lower abdominal pain and sterility. Menstruation had begun at twelve, and had been regular every four weeks, the flow lasting five days. In 1929, tonsillectomy had been done and a year later a pilonidal sinus excised. She was married in 1930. Shortly afterward there developed a dull pain in both lower abdominal quadrants which persisted to the time of admission. The pain was worse on motion such as walking or bending and at the menstrual periods.

Examination revealed moderate tenderness on deep pressure over both tuboovarian regions. Muscle spasm was not elicited. No abnormality was noted in the urethra, Skene's or Bartholin's glands. The uterus was anteverted, of normal size, and movable with some pain. Both adnexa were thickened and tender but no definite masses were palpated. The cervix appeared normal and was free of discharge. On admission the temperature was 99° F. and the pulse 80.

Fig. 8.

Fig. 9.

Fig. 8.—Section of tube showing marked papillary proliferation of the epithelium in the lumen (microsummar).

Fig. 9.—Section of tube showing glands invading the subserosa, with surrounding cellular infiltration and nodular elevation of the overlying serosa (medium power).

Examination of the blood showed erythrocytes 4,250,000, hemoglobin 80 per cent (Sahli), and leucocytes 9,200. The differential count was normal. The urine showed a trace of albumin.

A preliminary diagnosis of chronic bilateral hydrosalpingitis was made. The uterus was first curetted and a very few tags of tissue obtained. At laparotomy the anterior surface of the uterus was spotted with numerous yellowish white pinhead-sized lesions suggesting tubercles. Both tubes were enlarged, thickened, and adherent in the culdesac and to the lateral and posterior surfaces of the uterus. On freeing the adnexa the adhesions bled profusely. The fimbriated extremities of both tubes were sealed. The ovaries appeared normal.

The pathologic report was as follows: Both tubes were enlarged and thickened along their entire lengths. The serous surfaces were injected and showed evidences of fibrous adhesions. Both fimbriated ends were closed. On microscopic examination (Fig. 8), the tubal mucosa showed in places marked papillary proliferation of the epithelium with distinct invasion and many glandular formations. Some sections

showed much leucocytic exudate in the lumen and between the invading epithelial processes. All layers contained mature glands some of which had undergone cystic dilatation. Scattered leucocytes were present in many of the gland lumina, in the interstitial spaces between the smooth muscle fibers and in the subserous layer. In some areas there was a marked cellular infiltration about the glands. These glandular units were in many places located directly beneath the serosa, producing distinct nodular elevations of the surface (Fig. 9). Here and there were seen somewhat isolated glands without cellular reaction about them. These were more common in the subserosal layer. The diagnosis was infiltrating carcinoma, apparently of the glandular type with a tendency to papillary formations, especially in the mucosa and in a few subserous lymph vessels.

Following her operation, the patient was lost sight of until one year later. When examined in the Out-Patient Department on Sept. 18, 1933, she had no complaints. She had gained weight and was free of abdominal distress. The uterus was found in normal position and was movable without pain. No adnexal masses were palpated and no carcinomatous infiltrations could be detected.

DISCUSSION

While the etiology of carcinoma of the fallopian tubes is unknown, consideration has been given to two chief possible predisposing factors: preexisting inflammation and benign papilloma. Evidences advanced in favor of the first are the high incidence of closed fimbrias and the comparatively high rate of sterility. Evidence in favor of the second is chiefly by inference.

Our own cases offer little in settling this problem. The patient in Case 3 had been treated for a right Bartholinitis three years preceding laparotomy. The patient in Case 4 had had bilateral lower abdominal pain of two years' duration. In the other two cases, a history of inflammation was lacking. The patients in Cases 1, 3, and 4 had been sterile and the patient in Case 2 had had one child twenty-one years before. In all four cases the fimbriated ends of the tubes were sealed. Pathologically there was evidence of chronic inflammation in the patients of Cases 2, 3, and 4. In none of them was there convincing evidence of a preexisting benign papilloma which had undergone a malignant change.

The symptom picture is inconstant. Even at laparotomy the lesion is often unrecognized and a tubal enlargement is suspected of being inflammatory rather than malignant. Reported cases show that the diagnosis is usually made by microscopic examination of the removed tissues.

In our own series, a correct preoperative diagnosis was not made. At operation, only Case 2 was recognized as carcinoma. Cases 1 and 4 were thought to be hydrosalpingitis and Case 3, tuberculous salpingitis.

To increase the incidence of diagnosis, it would seem of first importance that the possibility of tubal carcinoma be kept constantly in mind. At times, the disease may be suggested in a woman beyond forty with

a history of irregular bleeding or a brownish or bloody discharge and in whom curettage has brought away little or no membrane. This was true in Case 2 of our series. As suggested by Falk,[3] the diagnosis may be made from the examination of tissue removed by vaginal puncture. However, it is probable that this procedure would be of no value, except in advanced cases. A point well made, is the suggestion of Gupta[4] that at operation, all tubes be opened and inspected for papillary growths.

The prognosis is unfavorable. Weibel[5] placed the chance of cure with operative treatment at 4 per cent. Wechsler[6] in a review of a large series mentioned only 6 patients having no recurrence three or more years after operation. Jahkola[7] reported two cases of patients that were well after seven years, and Haupt,[8] one case of a patient that was cured and was well twenty years later. In our own group, the patient in Case 1 died within the first year. The remaining patients are alive and apparently well three years and eight months, three years, and one year, respectively, after laparotomy.

The treatment generally accepted is panhysterectomy and bilateral adnexectomy followed by irradiation. In the younger woman, opinion differs as regards the conservation of the uninvolved cervix and ovaries. In the present series, treatment was conservative because the condition was not recognized at the operating table. Only in Case 2 where the nature of the lesion was apparent, was there radical excision. Postoperative irradiation was given in Cases 2 and 3. The patient in Case 1 died before the treatment was begun, and the patient in Case 4 failed to return for follow-up care.

SUMMARY AND CONCLUSIONS

1. Four additional cases of primary carcinoma of the fallopian tube, including the two youngest on record, are reported.

2. The significance of inflammation as an etiologic factor remains disputed. Three of our four patients showed evidence of chronic inflammation.

3. A clinical diagnosis is extremely difficult. Hope for increasing these diagnoses lies in keeping the possibility constantly in mind.

4. At operation the lesion many times simulates chronic tubal inflammation or tuberculosis from which conditions it must be differentiated.

5. Opening of all tubes at the operating table and their inspection for papillary growths as advised by Gupta, would at times aid in the diagnosis and in the institution of the proper surgical treatment.

6. A negative curettage with a history of irregular bleeding or a brownish or bloody discharge is, in a woman beyond forty, suggestive of tubal carcinoma. In such cases the adnexa should be carefully palpated for enlargements.

REFERENCES

(1) *Orthmann, quoted by Boxer:* Monatsch. f. Geburtsh. u. Gynäk. **30:** 549, 1909. (2) *Johnson, W. O., and Miller, A. J.:* Ann. Surg. **93:** 1208, 1931. (3) *Falk:* Therap. Monatsch. **11:** 311, 1897. (4) *Gupta, N.:* J. Obst. & Gynec. Brit. Emp. **38:** 839, 1931. (5) *Weibel, W.:* Med. Klin. **26:** 117, 1930. (6) *Wechsler, H. F.:* Arch. Path. & Lab. Med. **2:** 161, 1926. (7) *Jahkola, A.:* Acta Soc. Med. Fenn. duodecim (Ser. B. No. 2) **16:** 1, 1931. (8) *Haupt, W.:* Zentralbl. f. Gynäk. **57:** 742, 1933.

TREATMENT OF UNILATERAL URINARY FISTULAS BY X-RAY DESTRUCTION OF THE KIDNEY

A Clinical and Experimental Study

Nathan P. Sears, Ph.B., M.D., Syracuse, N. Y.

NO MORE trying condition exists for either patient or surgeon than fistulas of the ureters and kidneys, especially when these organs have been the seat of long-standing infection. In many instances nephrectomy is the only means for cure and may be extremely hazardous for those already exhausted by previous infections and surgery.

In 1928 Klein[1] was successful in treating by x-ray four patients who had developed ureteral fistulas following the Wertheim operation for carcinoma of the cervix. Each fistula had persisted for three months and was inoperable because of extensive ureteral damage. Ninety per cent H.E.D. (unit skin dose) was given anteriorly and the same posteriorly. In two of the patients the fistulas closed in about three weeks, and in two a second series of treatments was necessary.

Since Klein's report appeared, Conrad,[2] Halbfas-Ney,[3] Soiland,[4] and Sénèque[5] have successfully treated ureteral and renal fistulas with irradiation. Soiland also produced clinical cures in cases of renal tuberculosis by this agent. Stoeckel[6] was unable in two cases to heal fistulas by Klein's technic and questioned whether Klein's success was due to kidney destruction or to some unknown action upon the fistulous tract.

My report presents an unusual type of urinary fistula healed by irradiation.

Mrs. C. B., white, aged forty-nine years, was seen at the Syracuse University Hospital on Feb. 13, 1930. She had suffered for seven years with urinary pain and frequency, pain in the left side radiating from the loin downward, and blood in the urine. An x-ray picture made several years before had shown a shadow in the region of the left kidney. Recently she had developed fever, weakness, and a generalized rash. There was no history of venereal infection. Menstruation had ceased with irradiation for uterine myomata several years ago. Physical examination showed a diffuse macular rash covering her entire body. The patient appeared weak and to have very little resistance. There was tenderness and muscular rigidity in the left flank. No mass was palpable. Blood cell count was normal; N.P.N., 30 mg.; phenolsulphonephthalein, 55 per cent for two hours. There was albumin, pus, and blood in the urine, and the Wassermann test was 4 plus with both antigens. In spite of the positive Wassermann, the rash was considered a toxic dermatitis by a consulting dermatologist. Cystoscopic examination, twice repeated, showed a left

pyonephrosis with probable stone. No dye appeared from the left kidney in fifteen minutes on either occasion. Because of the patient's general condition and especially because of the generalized, ugly-looking rash, I decided to delay operation and attempt to reduce the infection. Considerable general improvement occurred, and the rash disappeared after several irrigations of the left kidney. On Mar. 18, 1930, she was admitted to the Syracuse Memorial Hospital and on March 29, the following operation was performed:

The usual left lumbar incision was made. After dividing the perirenal fat, the greatly distended and thickened renal pelvis was exposed. The ureter was located, clamped, and divided and the stump carbolized. In freeing adhesions around the kidney, a cavity filled with foul purulent urine was opened, and this escaped into the wound. A careful attempt was then made to expose the rest of the kidney. It was then quite certain that the kidney was partially rotated so that the convex surface lay toward the back and the pelvis toward the anterior abdominal wall. After considerable effort, a pulsating vessel, apparently the renal artery, was found entering the mass just above the upper border of the pelvis. This was doubly clamped, divided and tied. The veins were not definitely identified. As the pelvis was incised and explored, only a thick-walled, pus-filled cavity was found. There was very little kidney substance. With a finger within the cavity, its walls were carefully dissected free and removed. During the dissection, a piece of firm tissue about 5 cm. by 2 cm. was found densely adherent to the aorta. To dissect this free was almost certain to produce an uncontrollable hemorrhage. This situation brought the decision to go no farther with the dissection, and, if a fistula developed, to destroy any remaining kidney tissue with x-ray. The wound was closed in layers, with a drain in the upper angle. After operation the patient was in good condition, having been on the table forty-five minutes.

A fistula did develop and it drained profusely. It seemed as if more urine saturated the dressing than was excreted by the normal kidney. Irradiation was decided upon. From May 8 to 17, 1930, $2\frac{2}{5}$ E.D. (Machine setting 156 KVP, 4 ma., 1 mm. Al, ¼ mm. cu. distance 20 in.) were given, divided equally between the anterior and posterior surfaces of the left kidney region. At first there seemed to be an increased excretion of urine. In a few days, however, it began to diminish in amount. The patient left the hospital on May 20, 1930. She came to the office on June 9 rather weak but feeling otherwise well. A thin purulent discharge with a urinary odor continued from the wound, and on July 7 a probe entered the sinus 12 cm. The patient's condition was much improved. From July 7 to 10 she received a second series of x-ray treatments identical with that given in May. Following this she left Syracuse for the summer. She returned on Dec. 26, 1930. The wound was still draining. She had gained more than ten pounds and felt better than she had for many years. The wound was probed and cauterized several times with no improvement. On Jan. 12, 1931, the sinus was opened and found to be 10 cm. deep. At the bottom was a cavity 2.5 cm. in diameter filled with foul urine, but no evidence of kidney noted. This operation failed to improve the condition, and from Jan. 30, 1931, to Feb. 10, 1931, she received 3 E.D. making a total of $7\frac{4}{5}$ E.D. at the surface, or an estimated dose at the kidney of 4 E.D. On Feb. 7, 1931, she was discharged perfectly well and has remained so. (Last seen December, 1932.)

Experimental Observations.—Since 1903, when Heineke[7] first studied the effects of x-ray upon the kidney, considerable literature on this subject has developed. I will quote from only those articles which seem more pertinent to this report.

In 1927 Willis and Bačhem[8] irradiated the kidneys of twelve dogs through an aluminum-lined (1 mm.) lead tube 6½ in. long and 2½ in. in diameter passed to

the kidney through a midline incision. They used 140 KV, 5 ma., 2 mm. of aluminum filter and a distance of 11 in. Six minutes' exposure equalled one human E.D. They found a breaking down of the tubules and replacement with new connective tissue. In spite of marked changes in the tubules, the glomeruli remained practically unaltered.

Klein at the time he reported his clinical experience also reported experiments on three cats and one dog. He exposed these animals to the same dose used on his patients (90 per cent H.E.D. both anterior and posterior). Three weeks later he killed the animals and found shrunken glomeruli and scar tissue between the tubules.

Hartman, Daub, and Bolliger,[9] who have published several reports concerning the effect of x-ray on the kidney, presented in 1927 a report on the relative susceptibility of the various viscera and concluded that the kidney is the most sensitive and that the others are affected in the following order: intestine, stomach, pancreas, ovary, spleen, lungs, adrenal and liver. They warn that the kidney must be carefully considered when applying x-ray therapy to abdominal disease, especially in the young individual.

One of the most complete reports on the subject of x-ray destruction of the kidney appeared in 1932 after my own experiments were completed. Enger and Preuschoff[10] using four dogs carried out a most detailed study of urinary secretion, blood chemistry, and anatomic changes. They exposed an area 17 cm. by 17 cm. over the back at the costovertebral angles. Each dog received from 60 per cent to 140 per cent H.E.D. at a time, at intervals of from one week to three months, making a total of from 5.8 to 21 H.E.D. per animal. I will refer only to the anatomic changes as described and quote from their conclusions: "The anatomic examination disclosed a marked shrinking of the kidneys, which was not present in equal degree on both sides. The cortex and medulla shared alike. The histologic examination shows marked changes in the tubules, swelling and desquamation of the epithelium. Marked changes in the glomeruli (hyalinization) and in the vessels (endarteritis) were very rarely observed." They noted especially that both kidneys were not equally affected and explained it as due to the asymmetrical position of the dog on the table. This interpretation was supported by the fact that the skin destruction varied in the same manner.

My own experiments were begun in July, 1931, and were performed to determine whether or not it was likely that the x-ray had actually destroyed the diseased kidney left in my patient. It seemed possible that healing might have taken place through the action of the rays upon the fistulous tract. Up to that time no attempt had been made experimentally to destroy completely an animal's kidney.

EXPERIMENTS

The right kidneys were removed from six healthy rabbits. They, as well as two control animals, were numbered and placed in individual cages. No attempt was made to make any study of kidney function or blood pressure. Three months after operation the six nephrectomized animals were prepared for irradiation; the fur on the anterior abdominal wall over the left kidney was clipped away, the animal anesthetized with urethane and morphine and fastened on his back to an operating board. The left kidney was located, brought under the surface of the abdominal wall and held by two ring clamps. These were so applied as not to injure the kidney or shut off the circulation and yet bring the kidney directly under the x-ray. The rest of the animal was completely protected by heavy sheets of lead. The factors of x-ray were 106 KVP, 4 ma., 10 in. distance and 1 mm. aluminum filter. This

produced 2 E.D. in sixteen minutes and twelve seconds. The first irradiation was administered on Oct. 7, 1931, and the last on Oct. 20, 1931. Two E.D. were given each rabbit at each exposure. Animals No. 1 and No. 2 received 2 E.D., No. 3 and No. 4 received 4 E.D., and No. 5 received 6 E.D. While No. 6 was being anesthetized for the last exposure, he had a convulsion and died a few hours later, apparently from an air embolism.

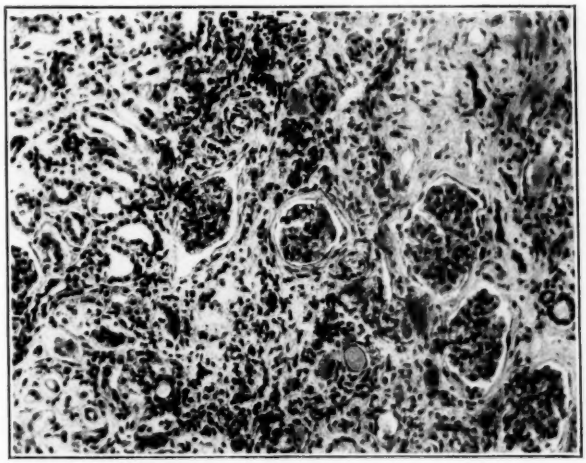


Fig. 1.*—(Photomicrograph ×150.) Section of kidney receiving 2 E.D. Several glomeruli surrounded by fibrous connective tissue are seen. To the left are some tubules showing only slight destructive changes. At center and right the tubules are completely replaced by connective tissue. In the center are several groups of round cells and a few dilated capillaries.

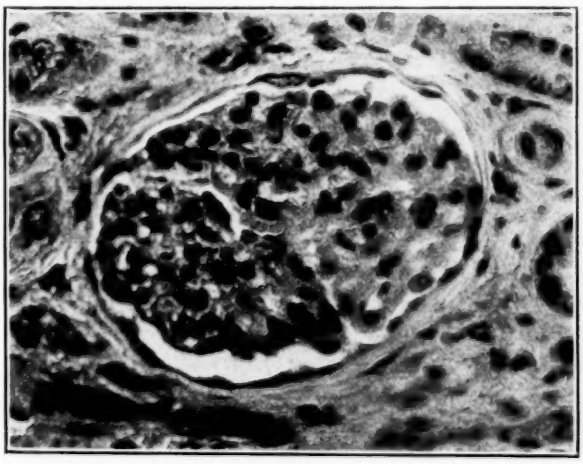


Fig. 2.—(Photomicrograph ×580.) Area from same section as Fig. 1. The glomerulus in the center is seen to be surrounded by fibrous connective tissue. To the left, an edge of a tubule showing cloudy swelling is seen. In the lower left destroyed tubules showing some degeneration are seen. Nuclei in the glomerulus show hyperchromatosis.

On Feb. 6, 1932, No. 4 died, an autopsy was performed and the kidney placed in Zenker's solution. On Mar. 2 the other animals were killed, the kidneys removed

*Photomicrographs by the Photographic Department of Syracuse University College of Medicine.

and placed in Zenker's. The specimens were embedded in paraffin, cut, and stained with hematoxylin and eosin.

The kidneys which had received 2 E.D. (Figs. 1 and 2) showed scattered areas of involvement; in these areas the glomeruli showed varying stages of fibrosis and atrophy, and the capsular spaces in some instances appeared occluded. There had been apparently rather marked tubular destruction in these areas, with fibrosis and

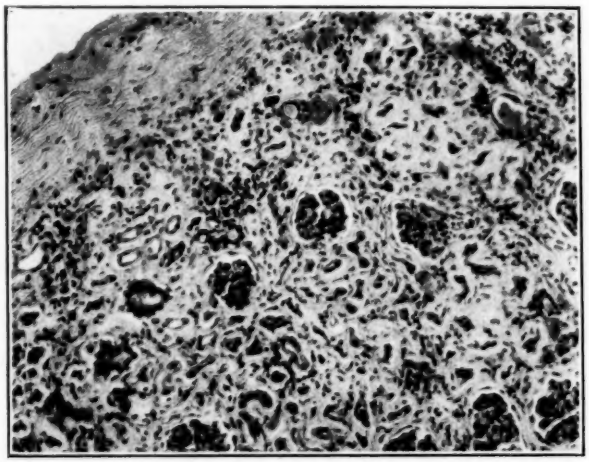


Fig. 3.—(Photomicrograph ×150.) Section of the kidney receiving 4 E.D. In the upper left is seen part of the thickened capsule. There is periglomerular fibrosis to a marked degree. Scattered partially degenerated tubules make up the background, most of the epithelial structure having been replaced by connective tissue. Groups of round cells and dilated capillaries also present.

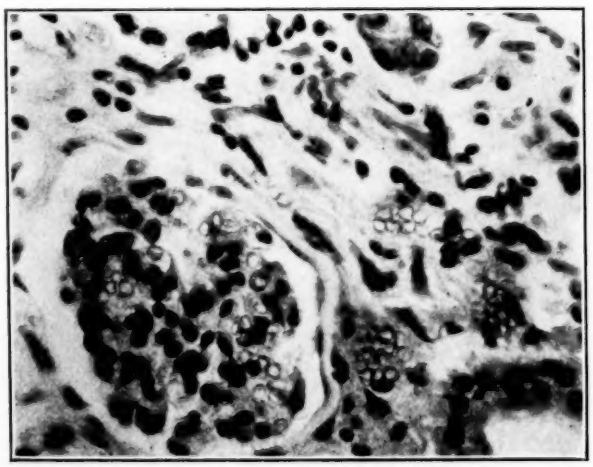


Fig. 4.—(Photomicrograph ×580.) Area from the same section as Fig. 3. The connective tissue is abundant. Toward the upper right is seen partial regeneration of a damaged tubule. In the lower right is the edge of a hypertrophied tubule (compensatory). Blood capillaries and round cells are present.

considerable round cell infiltration. The remaining kidney tissue showed no definite change aside from a few scattered areas of cloudy swelling of the tubules.

Sections of the kidneys which had received 4 E.D. (Figs. 3 and 4) showed the same processes present to a much greater degree. There appeared to be marked tubular destruction with subsequent partial regeneration and fibrosis. In some areas

the entire tubular structure was destroyed. The glomeruli showed chiefly a fibrosis of the capsule with some slight hyaline change, but in general the involvement was much less than that of the epithelial structure. The surviving convoluted tubules showed varying degrees of degenerative change. There was a diffuse round cell infiltration.

In the section from the kidney which had received 6 E.D. (Figs. 5 and 6)

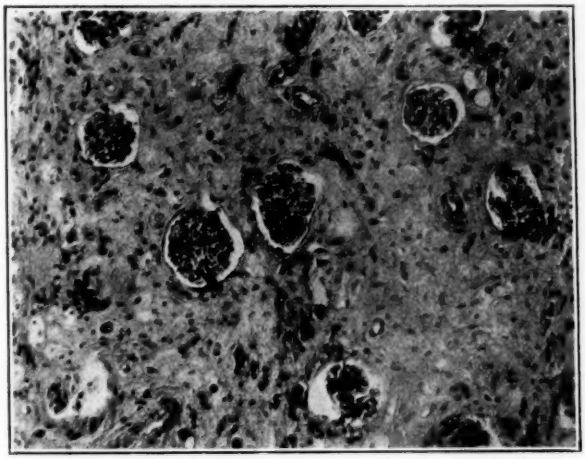


Fig. 5.—(Photomicrograph ×150.) Section of kidney having received 6 E.D. Here the glomeruli appear more numerous because of the marked replacement of the epithelial structure by connective tissue. Dilated capillaries and groups of round cells are less numerous than in Fig. 3.

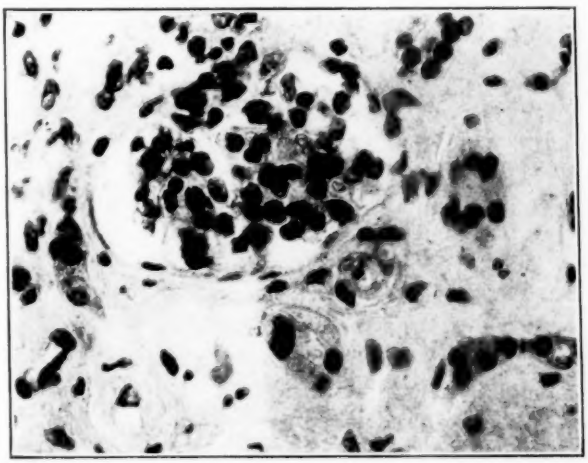


Fig. 6.—(Photomicrograph ×580.) Area from same section as Fig. 5. Marked hyperchromatosis of the glomerular nuclei. All tubules replaced by connective tissue. No dilated capillaries and very few round cells seen. Here, as in Fig. 5, the process is about complete, only scar tissue remaining to surround the glomeruli.

the tubular destruction, with subsequent fibrosis, was much more marked; the glomeruli showed comparatively little involvement aside from capsular fibrosis and widening of capsular spaces. The surviving tubular epithelium showed the same degenerative changes as in the other sections, with scattered areas of apparent compensatory hypertrophy. There was a rather diffuse hyaline degeneration of the

interstitial tissue with comparatively slight round cell infiltration. Aside from the hyaline degeneration in this section, the large blood vessels showed comparatively little change. Areas from the medulla (Fig. 7) showed almost complete replacement of the collecting tubules by connective tissue.

DISCUSSION

From both experimental and clinical evidence, it is apparent that modern x-ray therapy can destroy normal and diseased kidneys. The intricate epithelial structure of the kidney is replaced by connective tissue. The vascular and glomerular units are the last to be affected. That the application of x-ray is safe seems acceptable since the kidney is the most susceptible of the abdominal viscera (Hartman, et al.). The technic should be accurate and under the direction of an expert roentgenologist. The location of the kidney should be carefully de-

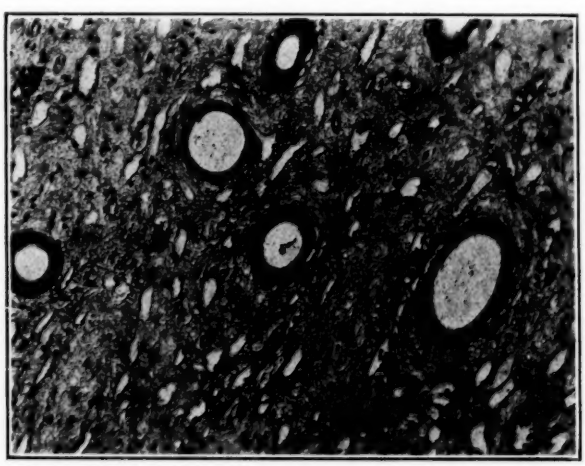


Fig. 7.—(Photomicrograph ×150). Section from the medulla of kidney having received 6 E.D. Practically all epithelial structure replaced by connective tissue in medulla also. Sections of four or five dilated collecting tubules are seen.

termined so that it will receive all the rays intended for it. This is emphasized by the observation of Enger and Preuschoff that in their animals both kidneys were not equally affected due apparently to the fact that owing to the dog's position on the table the kidneys did not receive an equal amount of x-ray.

SUMMARY

1. A brief résumé of the literature concerning the effect of x-ray on the kidney is presented.

2. A case of renal fistula cured by irradiation is reported.

3. Experimental evidence of the effect of irradiation on the rabbit's kidney is presented showing that x-ray produces a marked destruction of the normal kidney structure followed by replacement with connective tissue.

4. X-ray in properly selected cases is shown to be a definite and safe aid in the treatment of unilateral urinary fistula where surgery is impossible or unwise.

The irradiation, both clinical and experimental, reported in this paper was under the direction of Dr. Foster C. Rulison, roentgenologist to the Syracuse Memorial Hospital.

I am indebted to Dr. J. Howard Ferguson, associate professor of pathology at Syracuse University College of Medicine, for his help in interpreting the experimental lesions produced.

REFERENCES

(1) *Klein, P.:* Strahlentherapie **28:** 482, 1928. Abstr. Zentralbl. f. Gynäk. **52:** 1500, 1928. (2) *Conrad, G.:* Zentralbl. f. Gynäk. **53:** 2520, 1929. (3) *Halbfas-Ney, P.:* Ztschr. f. Urol. **24:** 734, 1930. (4) *Soiland, A.; Castolow, W. E.; and Meland, O. N.:* California & West. Med. **30:** 93, 1929. (5) *Sénèque, J.:* Presse méd. **36:** 1330, 1928; also Abst. J. A. M. A. **91:** 1930. (6) *Stoeckel, W.:* Monatschr. f. Geburtsh. u. Gynäk. **87:** 21, 1931; also Abst. J. A. M. A. **96:** 1554, 1931. (7) *Heineke:* München. med. Wchnschr. No. 48, 2090, 1903. (8) *Willis, D. A., and Bachem, A.:* Am. J. Roentgenol. **18:** 334, 1927. (9) *Daub, H. P.; Bolliger, A.; and Hartman, F. W.:* Radiology **8:** 142, 1927. (10) *Enger, R., and Preuschoff, P.:* Virchows Arch. f. path. Anat. **283:** 489, 1932.

505 Medical Arts Building

THE TREATMENT OF FIBROIDS*

A Report of a Series of 443 Cases

W. C. Danforth, B.S., M.D., F.A.C.S., Evanston, Ill.

(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

THE frequency of fibromas of the uterus causes the treatment of these tumors to be an important part of the work of the gynecologist. Statistical estimates from various clinics of the frequency of their occurrence vary according to the material dealt with, but it seems to be fairly well agreed that after the age of thirty-five about 20 per cent of all women have fibroid growths in the uterus. Many of these are small and unimportant clinically but the number which require attention is sufficiently large that gynecologic surgeons in active practice must deal constantly with them. I wish to discuss the results of our management of these tumors during recent years. The present report deals with a series of 443 consecutive cases cared for in the Department of Obstetrics and Gynecology of the Evanston Hospital. We have included in this series only those patients cared for during the past few years, during which time we have followed a definite operative technic to which we have become accustomed. It therefore permits conclusions to be drawn as to the results which may be expected today. This series includes only those patients for whom some form of treatment seemed necessary for the tumor itself and does not include a large number of cases of fibroid growths which were without symptoms and which did not require treat-

*Read at a meeting of the Chicago Gynecological Society, February 16, 1934.

ment. This series also does not include patients in whom operation was primarily done for some other condition and in whom small fibroid growths were found.

We are accustomed to divide fibroid tumors into three classes:

1. Those which need no treatment.
2. Those which may be irradiated.
3. Those which should be operated upon.

It should be quite clearly understood that when a case is assigned to the first class, that is, to the group which need no treatment, that this case does not necessarily remain permanently in this class. All women who are advised that operation or other treatment is not immediately needed should also be told that examination should be repeated at intervals and that any increase in menstrual flow should be reported. A number of the cases reported in this series were women who when first seen needed no intervention but who later, because of increase in the size of the tumor or the onset of menorrhagia, were operated upon.

In this series, 93 cases, or 21 per cent, were irradiated. Cases for irradiation should be chosen with painstaking care. We very much prefer the use of radium to x-ray. The latter was used only twice in this series. In both instances the patients were poor subjects for even trifling surgical procedures or for anesthesia.

I believe that radium is preferable to x-ray therapy, first, because with radium only the pelvic organs themselves are subjected to irradiation while when x-ray is used the whole lower body, parietes, bladder, and a portion of the enteron are subjected to its influence. Second, because prior to the introduction of the radium capsule, the patient being anesthetized, a careful pelvic examination may be made which may give information which the operator has not obtained earlier. Third, the introduction of the radium capsule should always be preceded by a diagnostic curettage which will reveal the presence of corporeal carcinoma. This is not an infallible procedure but its value is sufficiently great that it should never be omitted.

It is a mistake to regard the use of radium as an innocuous procedure or one which may lightly be used. Its contraindications have been stated in a previous communication. The contraindications which we are accustomed to observe are as follows:

1. *Age.*—The woman should be over forty and the farther past that age the better. Of late years we have been less willing to irradiate women who have just entered the fifth decennium and have reserved this mode of attack for older patients. The amount of irradiation which is required to control bleeding is sufficient to destroy ovarian activity. This should not be done until the woman is at or not far from the age of the menopause. It is far better that younger women should be operated upon. For them surgery is less radical than irradiation.

2. *Past or Present Inflammatory Adnexal Disease.*—The presence of inflammatory disease or the history of its previous existence should exclude the use of radium. This may be lighted up by the trauma of the dilatation and curettage which precedes the introduction of the radium or by the changes produced in the uterus itself by

TABLE I. AVERAGE AGES, CLASSIFIED ACCORDING TO TREATMENT

All cases treated	42.1 years
Hysterectomy, adnexa preserved	41.6 years
Irradiated	47.3 years
Hysterectomy, adnexa removed	44.5 years
Myomectomy only	36.4 years

the radium. The extensive necrosis of the mucosa and submucosal structures produced by irradiation, and which may be seen in a uterus excised for any reason a week after irradiation, is convincing evidence that radium is an active substance.

3. *Size.*—Our own custom is to limit the use of radium to small growths. A rule which is commonly stated is that irradiation should not be used in tumors larger than a three months' pregnancy. Of late we have restricted the choice of tumors for irradiation on the basis of size even more strictly and have rarely irradiated growths larger than a pregnancy of two and one-half months. This appears to be in accord with the experience of most writers although a few have extended the use of irradiation to larger growths. It also seems wise not to irradiate tumors which are notably irregular in shape.

4. *Ovarian Neoplasms.*—If ovarian growths are present, it is wiser to abstain from irradiation.

5. *Adhesions in Pelvis.*—If the patient has some previous time undergone an operative procedure which may have left adhesions in the pelvis, it is best to abstain from the use of radium. In the normal abdomen the peristaltic movement of the intestinal coils prevents any limited area of the bowel being continuously exposed to the radium rays. If a bowel coil is held by adhesions so that it remains fixed in one spot, the bowel wall, if within the effective range of the radium rays, may receive serious damage.

6. *Submucous Fibroids.*—These growths, if recognized, should not be irradiated. If they protrude into the uterine canal, they are often at least partially necrotic. If they have been extruded into the uterine canal, particularly if the internal os is dilated, they are usually infected. In either case they are not favorable cases for radiotherapy.

7. *Pelvic Pain.*—Pain in the pelvis should exclude the use of radium. It may be produced by a rapidly growing tumor, by adhesions from some previous inflammatory state or by an unsuspected pelvic inflammation. In any case irradiation should be avoided.

8. *Retrodisplacement.*—If a marked retrodisplacement is present we prefer to refrain from irradiation fearing that the curettage and introduction of the radium capsule may cause material from the uterine cavity to drip into the peritoneum. This is not a grave danger and prior to the inclusion of retroversion in our list of contraindications we irradiated a goodly number of retroverted uteri without serious incident. None the less the possibility of trouble causes us to feel easier when these cases are excluded.

9. *Radiophobia.*—It does not seem wise to insist upon radiotherapy when the patient fears it. Often individuals are encountered who, usually because of knowledge of death from carcinoma of a woman who had been treated by irradiation, have a marked fear of radium. It is better to treat these women surgically.

The small fibroids which are treated by irradiation usually demand attention because of bleeding. It is probable that in many instances the menorrhagia is due to the oncoming menopause and that the small growth is merely incidental. If careful selection of cases is made, with due regard to the contraindications already stated, extremely satisfactory results will be attained.

If operative treatment is decided upon, the character of the procedure must be considered. In this report we are considering primarily our results with abdominal hysterectomy, which, in the opinion of most writers in this country, is the preferable mode of attack in the majority of cases. We have made use of vaginal hysterectomy only when dealing with small tumors, usually when some form of vaginal plastic work was indicated. These are not included in this series nor have we included a considerable number of cases in which pedunculated tumors, extruded or about to be extruded through the cervix, were removed. It should be strongly emphasized that when dealing with these masses which have been forced through the cervix or which are in the process of being delivered, that simple removal alone is all that should be done. The simplest and best method is to place a clamp upon the pedicle within the cervix, divide the pedicle and remove the growth, allowing the clamp to remain from twenty-four to forty-eight hours. If the mass is still within the cervix, one may wait until it is extruded or split the cervix anteriorly to gain access to it. Hysterectomy, abdominal or vaginal, should never follow at once. Other tumors which may be present may be dealt with some weeks later. These growths are always infected and from them bacteria have usually gained access to the uterine wall from which the pedicle springs. Invasion of the peritoneal cavity is gravely dangerous.

Myomectomy, or the removal of the tumor, allowing the uterus to remain, has a definite field of usefulness. In our own work it is carried out in younger women when the maintenance of reproductivity is highly desirable and when the relationship between the tumor and the uterus is such that it is technically possible to remove the tumor and leave a uterus which is capable of pregnancy. It is sometimes possible to remove a number of tumors and leave a uterus in excellent condition. The patient should always be warned of the possibility of similar growths appearing later. Desire to retain the uterus should not lead one to extend the procedure beyond its proper limits or to risk leaving a uterus which is the seat of many deep wounds. Careful and nontraumatic enucleation of the growth, meticulous hemostasis and painstaking suture of the uterine wounds are essential for the best results. Careful closure of the wound edges, to prevent so far as is possible the formation of adhesions, is important.

We believe that myomectomy during pregnancy is, in most cases, unwise. We prefer to leave the tumor and deal with the situation pre-

sented by the pregnancy and the fibroid on its merits at term. In many instances the fibroid, because of its size and location, is of little or no importance in the management of the pregnancy. Attempts to enucleate growths from the wall of the pregnant uterus are often accompanied by severe bleeding which is difficult to control. A deep-seated tumor, if removal is attempted, involves the risk of opening the uterine cavity. Conservatism during pregnancy is the safest course.

In the majority of the operated cases in this series hysterectomy was done. This may be of the total or subtotal type with or without the excision of the adnexa. Whenever possible both ovaries were preserved and both ovaries were not excised unless the preservation of one was unwise. The younger the patient the more essential it is to preserve ovarian function and in our very recent work we have been even more particular than we formerly were to avoid total ablation of the ovaries. Reference to Table I will show that while the average age of all patients was 42.1 years the average age of those women both of whose ovaries were removed, was 44.5 years, and the average age of those who were irradiated was 47.3 years.

Total hysterectomy is chosen only in those cases in which the cervix is notably diseased or in which some fear is felt of an early coincident malignancy.

TABLE II. SUMMARY—OPERATIONS AND IRRADIATIONS, 443 CASES

	CASES	PER CENT
Irradiated	93	21.0
Subtotal hysterectomy, adnexa not removed	137	31.0
Total hysterectomy	18	4.0
Myomectomy only	28	6.3
Subtotal hysterectomy plus both tubes and ovaries	74	16.7
Subtotal hysterectomy plus partial removal of adnexa	93	21.0

Considerable difference of opinion has existed as to the comparative value of total and subtotal hysterectomy. The importance of the question depends almost wholly upon the danger of the development of carcinoma in the retained cervical stump. It is altogether probable that in many cases in which cancer appears in the cervical stump after hysterectomy, particularly when the carcinoma appears soon after hysterectomy, the malignant growth was present and unrecognized at the time of operation. In this series we know of no case in which carcinoma appeared in the stump after subtotal hysterectomy. In a recent review Gardner and Finola quote a number of authors concerning the frequency of carcinoma in the retained stump as follows: Polak 2 per cent, Prestini 0.5 per cent, Tesauro 0.54 per cent, Hartman 2 per cent, Hoehman 0.27 per cent. The 1,114 cases studied by Hoehman were taken from the records of the Woman's Hospital, New York, the work being done under

the supervision of Ward. The conclusion reached was that, at least in the hands of the average operator, the increase in the operative risk which accompanies the use of the complete operation is greater than the later risk of the development of carcinoma. In one case a carcinoma of the body was present and unrecognized. The retained stump was treated by irradiation and the woman remains well and apparently free from recurrence after four years. In all cases in which doubt exists as to the presence of carcinoma, and if subtotal hysterectomy has been done, the excised uterus should be opened before completing the operation. Should anything suggestive of malignancy be found the cervix may be immediately removed.

TABLE III. IRRADIATION OR ABLATION OF OVARIES

	CASES	PER CENT
Irradiated	93	21.0
Total hysterectomy (ovaries excised)	17	3.8
Subtotal hysterectomy (ovaries excised)	74	16.7
Total cases ovaries removed or destroyed	184	41.5

Subtotal hysterectomy should always be preceded by careful study of the cervix and should only be done when the cervix is quite innocent in appearance. In expert hands the mortality of total and subtotal hysterectomy is about the same. In the hands of the occasional operator the danger of injury to the bladder and ureters and the greater risk of contamination of the peritoneum increase the risk of the operation considerably.

TABLE IV

Operated cases only	350
Ovaries excised	91
Percentage ovaries excised	36 per cent

Frequent use of the more extended operation should not be made by those whose operative experience is small. Should the cervix present notable evidence of endocervicitis and ectropion, it is possible to do a cervical plastic procedure and a subtotal hysterectomy at the same sitting. By this means a healthy cervix may be left without the necessity of opening into the vagina from above. In cases in which nothing is done to the cervix at the time of operation, later cauterization of the cervix may be helpful, particularly if some discharge persists. We have excised the retained cervix in a few cases in only two of which we had previously removed the uterus. One of these, very recently, bled severely from the stump, packing being necessary to control the bleeding. A biopsy showed no carcinoma. Immediate excision of the cervical stump was done. It is probable that injury to a vessel caused by infection in

the stump caused the hemorrhage. In another case a little bleeding was caused by a polyp which developed in a retained stump about eighteen months after operation. Removal of the polyp gave immediate relief.

TABLE V. MORTALITY

Total number	443
Death	1
Mortality	0.23%
Operated cases only	350
Mortality	0.28%

In this series one death occurred, giving a mortality of 0.23 per cent. Death was apparently from pulmonary embolism although, as autopsy was refused, the diagnosis could not be confirmed. The most satisfactory results are attained if operative work proceeds as expeditiously as is possible without the sacrifice of proper technic. The avoidance of trauma, and the minimization of blood loss are of great importance. In most cases, with good anesthesia, laparotomy pads are not needed. When their use cannot be avoided pieces of sheet rubber cause far less injury to the peritoneal surface than is produced by gauze pads.

It is evident that in experienced hands the risk of the surgical management of fibroids has become very small. Recent reports from well-known clinics show mortality rates of 1 per cent or less.

In clinics in which a considerable amount of work is done cases are often seen in which, by reason of great blood loss, the patients are less favorable subjects for operative work than would otherwise be the case. When a profound anemia is present and preoperative transfusion seems essential, we usually do this late in the day or in the evening and operate the following morning. This gives sufficient time for a reaction following the transfusion to occur if this is to take place. While this is a very valuable measure in severely compromised cases, we find it only occasionally necessary and do not hesitate to operate upon women with a marked anemia unless some condition is present which would cause the operation to be prolonged beyond the usual length of time. An operation lasting from twenty-five to forty minutes, with trauma reduced to the minimum and avoidance of blood loss is usually well borne by these patients. Lengthy procedures, with much handling of tissues, are not well endured.

We have felt that it is of great importance that the ovaries, or at least one ovary, be preserved. With increasing experience this opinion has become stronger. Even in women who are near the menopause the discomforts of that period are far less if ovarian tissue is preserved than if it is wholly absent. In younger women this is correspondingly more important. If the preservation of ovarian function is of importance it follows that it is essential that the operation be carried out in such a way

that the ovary will remain in good condition and continue to function. For this purpose it is necessary that a good blood supply be provided and the excision of the uterus is so carried out that the hilum of the ovary with its contained vessels is not disturbed. Experience has shown us also that women who, after operation, have the ovaries left normally mobile are more comfortable than those patients whose ovaries are firmly fixed to the cervical stump. The ends of the divided broad and round ligaments, therefore, are not attached to the stump of the cervix, unless this may be done without placing the attached ligaments under any strain. Experience in a far larger number of cases than are recorded in this series, as well as in many hysterectomies done for reasons other than the presence of fibroid tumors, convinces us that the argument that the support of the attached ligamentary stumps is necessary to prevent prolapse of the stump of the cervix and vagina is erroneous. On the other hand, too much tension, caused by attaching the broad and round ligaments to the cervix when in order to do so they must be drawn tight, is a cause of postoperative pelvic discomfort. Even dyspareunia may be complained of. The ovary is normally a movable organ and this normal mobility should, so far as is possible, be preserved after operation. The cervical stump also, after operation, should be freely movable and should preserve the mobility which is characteristic of the normal uterus.

The surgical treatment of fibroids is today in skillful hands a safe procedure. While the present safety of treatment and the possibility of affording relief with small risk to many women constitutes a tremendous advance it may sometimes appear, to one who has occasion to see many women with fibroids, that the safety of present-day management may occasionally cause some of the cases which could well remain, at least for a time, in the expectant list to be included among those for which operation is advised. Judgment as to the necessity for treatment, and if treatment is indicated, the selection of that method best adapted to the individual case is an important part of the duty of the gynecologist.

DISCUSSION

DR. RALPH A. REIS.—Dr. Danforth should be especially commended because of his very low mortality rate. His preference for supravaginal, or subtotal hysterectomy is about the same as that at Michael Reese Hospital. For many years there has been at this hospital a clientele that is largely Jewish. It is well known that Jewish women are relatively immune to carcinoma of the cervix or cervical stump. In recent years this clientele has been changing. Where formerly 90 per cent were Jewish, now less than 40 per cent are. Stimulated by the recent reports from New York and last year in Milwaukee from v. Graff in which such a large incidence of carcinoma of the cervical stump was reported, I made a survey of our cases from 1923 to 1933.

In 1923, 1.5 per cent of patients had total hysterectomy; in 1933, 14 per cent had total hysterectomy and 17.5 per cent had a vaginal hysterectomy. Therefore,

complete hysterectomy was done in 31.5 per cent of the patients, who were operated upon last year at Michael Reese Hospital.

In 1923, myomectomy was done in 19.5 per cent. In 1933 this was reduced to about 7 per cent.

The point Dr. Danforth made about the gradual decrease in the percentage of patients that are treated by irradiation is very much the same as the experience we have had at Michael Reese. Again comparing the years, 1923 to 1933, in 1923, 21 per cent of the patients were treated by irradiation. In 1933 this had dropped to 3.5 per cent. The drop had been made rather consistent because it was felt that surgery is very definitely more conservative than is irradiation. Seventy-five per cent of the patients at the hospital were forty-four years of age or under, were menstruating regularly and were showing no evidence of being in or at the menopause. It would seem then much more conservative to remove the fibroids that were producing symptoms and conserve if possible one or both ovaries.

Dr. Schmitz' figures show that approximately 8 per cent required reirradiation and 4 per cent of the fibroid patients required subsequent surgery. This would, I think, rather definitely speak for treatment of fibroids of the uterus by surgery in which the results are so nearly 100 per cent. Certainly the mortality rate is very low. Dr. Danforth's series showed one-fourth of 1 per cent mortality in 1933 in 144 patients. In Michael Reese Hospital there were no deaths in 1933 among 144 patients, and there was one death in 1923 in 75 patients.

There have been no evidences in the Michael Reese Hospital series that fibroids are associated with sterility. Eighty-three per cent of the patients who have been studied at the hospital gave a history of one or more full-term pregnancies; in other words, only 17 per cent of the patients at Michael Reese Hospital in those two years were sterile. The 3 per cent who were single were removed from that group, which reduces the sterility group to 14 per cent, which is surely no higher than for the average of women in general.

There were few fibroids noticed during labor. In the last 6,000 deliveries there were 9 patients with definite fibroids. Seven required no treatment and two had myomectomy performed at the time of cesarean section.

The thing of interest in this study is first, the rather large drop in those patients who were treated by irradiation and myomectomy. Supravaginal hysterectomy remains about the same. There has been during this time a definite increase in the percentage of patients who were so operated upon as to include the removal of the cervix. Total hysterectomy increased from 1.5 to 14 per cent and vaginal hysterectomy from 5 to 17.5 per cent.

DR. GEORGE H. GARDNER.—I wish first, to mention a problem related to those which Dr. Hillis has presented. Even after the abdomen is open, the surgeon may be sorely pressed to differentiate a pregnant uterus from one containing fibroids. Knowledge of the dates and character of recent menstrual periods is vital but careful inspection of the myomatous uterus frequently shows gross asymmetry as revealed by the sites of attachment of the round ligaments and tubes. Recently I operated upon a woman who had been told she was four months pregnant after an exploratory operation in a nearby city. By adequate exposure one could be certain the mass was made up of fibroids, among other reasons, the location of the round ligaments, tubes, and ovaries. They were attached in an unusually low position, behind the symphysis.

I wish that Dr. Danforth had told us of his postoperative morbidity, especially in regard to the incidence of phlebitis and embolism; are these complications more frequent nowadays?

I am in complete accord with Dr. Danforth's view that the preferable abdominal operation is subtotal (i.e., supracervical) hysterectomy; the entire uterus should be removed only when there is additional pathology such as cancer of the corpus or an unhealthy cervix with discharge. It would appear that the likelihood of cancer developing subsequently in a cervical stump has been greatly overemphasized.

Dr. Schmitz has had such an extensive experience in the use of roentgen rays and radium to arrest uterine bleeding that I hesitate to take issue with any of his conclusions. His advice to use radium for bleeding fibroids smaller than a three months' pregnancy and roentgen rays for larger masses certainly seems orthodox. His experience that 1,800 mc. of radium will permanently stop bleeding from a fibroid uterus is worthy of consideration, since it is common practice in some clinics to use smaller doses; this may account for certain unfavorable results. MacFarlane, of Philadelphia, has emphasized that persistent cryptic bleeding after radiation therapy should be treated preferably by surgery, rather than with more radium; with this principle I am in hearty accord.

Dr. Schmitz' comments on the use of roentgen rays to produce temporary amenorrhea are most interesting. I note that he recommends a 25 per cent smaller treatment for this purpose than to induce permanent amenorrhea. Is it true that these smaller doses of x-ray may induce not a temporary but permanent amenorrhea in a considerable number of young women who are then abruptly thrown into a premature menopause? Also, are the ovaries of others crippled by this decreased dose so that they fail to function normally afterward?

I am opposed to the use of radiation for the treatment of bleeding fibroids in women as young as thirty-six; I prefer to raise this age indication for radiation to forty-three, or better still, forty-five years. Ovarian activity must be conserved, if possible.

The problem of radiation therapy with x-rays or radium, in the treatment either of functional bleeding or of uterine fibroids is largely a matter of the indications for its use. Its effectiveness is due chiefly to a destructive action on the ovaries, and, consequently, in my opinion radiation has only a limited field of usefulness. It must be reserved for those patients (1) who are approaching the menopause, and (2) give no history or evidence of pelvic infection, and (3) have no adnexal pathology or (4) those who are poor surgical risks. In my experience, there are few cases of benign uterine bleeding which fulfill the above indications for radiation therapy. So far as fibroids are concerned, the satisfaction and feeling of security which follow their removal makes surgery far preferable to radiation except in the unusual case.

DR. JOSEPH L. BAER.—Dr. Danforth gave a very complete list of the contraindications for irradiation. Included in that list was the presence of adhesions. I wish to add that those adhesions may serve as nourishment to the fibroid, so that while a permanent amenorrhea may be achieved by irradiation, the adhesions between the tumor and the omentum and bowel will serve as a source of nourishment and the fibroid can continue to grow.

Twenty-five per cent of all uteri containing fibroids are in retrodisplacement, an additional reason for surgical removal. Destroying fibroids by irradiation does not relieve the retrodisplacement, a continuation of which results in additional pelvic pathology.

DR. N. S. HEANEY.—I have great respect for Dr. Schmitz' ability and knowledge in the use of radium but one thing I have always been unalterably opposed to is the use of radium in juvenile cases of so-called idiopathic menorrhagia. In not a single case have I ever given radium, although, some of these patients have at times been in desperate enough condition to require transfusions and several have

had one or more curettements. The great factor, so far, in the attention of these young girls is to carry them along as safely as possible conserving their blood and strength until such time as nature cures the menorrhagia. We know that these cases are undoubtedly due to a lack of glandular balance but what the particular factors are and how to treat the cause we have not as yet discovered. In the event that such a young girl finally requires a major procedure in order to make life safe or tolerable it would be much better to remove the body of the uterus and leave her ovaries uninjured than it would to give her curative doses of radium.

The age at which I prefer to give radium is when the patient is definitely in the menopause and has had already evidence of it, or when the menopause has already been established. I am giving radium in the treatment of benign disease very rarely at the present time.

If Dr. Danforth's contraindications for the use of radium in bleeding fibroids were carried out there would be very few cases left for radium. I should very much prefer to operate upon 99 per cent of the fibroids using radium for only those cases where operation would be a definite and serious hazard.

DR. FRED FALLS.—Malignancy is frequently associated with fibroids. In 128 patients that we had in the University of Iowa, considering those cases fibroids that entered with carcinoma in the stump of a uterus, the body of which had been removed for fibroids, and counting sarcoma that occurred in connection with fibroids and carcinoma that occurred in the body of the uterus as an incidental complication, we found 13.5 per cent of malignancy in 128 cases of fibroids.

Regarding the danger of operating on a fibroid of the uterus during pregnancy, one has to operate if a twisted fibroid is encountered. We have performed this operation in three cases, removing the fibroid with practically no hemorrhage and the pregnancy continued.

The question of retaining the ovary in connection with removal of the uterus depends not on the fibroid but on the ovary to be left. The amount of adnexal pathology depends on the type of patients that we are handling. At the Cook County Hospital 90 per cent or more of the cases have adnexal pathology. This makes our operation at Cook County Hospital of necessity more radical than it would be in a series of private patients.

There is one point that I think should be stressed, that is that some of these women have hyperthyroidism complicating the fibroid. Whether there is a relation between the two or not, I do not know, but that the two conditions can exist concomitantly I know very well. If one disregards the hyperthyroidism and operates on the fibroid, the patient is very apt to develop a serious thyroid crisis which may end fatally.

DR. CHANNING W. BARRETT.—We are coming back to the position that I have always maintained that the treatment of fibroids is surgical. The only question in regard to the treatment of fibroids is that of making surgeons who can take out fibroids with a mortality of 1 per cent.

I want to emphasize a point made by Dr. Danforth that it is never well to undertake complete removal of a uterus that has a polyp hanging out of the cervix. If that uterus needs to come out later you can make it a very safe procedure. If you take it out with the polyp it is a dangerous procedure.

DR. SCHMITZ (closing).—In the very beginning of my paper I stated that the cases selected for this study had definite indications for irradiation therapy. In the paper published in 1928 I showed that of all myomas only 11 per cent were subjected to irradiation treatment. Therefore we were even lower than Dr. Danforth in his material which was 21 per cent. Radiation therapy in benign hemorrhages is

a generally recognized and standardized method of treatment and, therefore, will remain a part of gynecologic treatment. There are a certain number of patients who are poor surgical risks, and there are always a certain number of patients who refuse operation. If these are added to those indicating radiation therapy there will remain quite a number of myomas needing radiation.

In the same paper it was shown that less than 30 per cent of benign bleeding uteri were subjected to irradiation. It is easily seen how many cases of bleeding uteri and myomas have been treated in some other way than by irradiation. The object of the paper tonight was to show what could be done with x-ray and radium in selected cases. I am quite sure the results obtained in this series of 433 cases were so good that I cannot see why there should be any objection at all to irradiation.

The question of the treatment of juvenile hemorrhages with either roentgen ray or radium is not an important one as only 7 were treated with radium and 13 with roentgen rays.

In the 122 myomas there were only three malignancies, namely, a pedunculated leiomyosarcoma; one patient returned three years later with a sarcoma; and in the third one malignancy of the rectum was diagnosed. In the bleeding uteri only two cases of carcinoma were found. The question of frequency of malignancy in myomas or bleeding uteri is not of any import, presupposing that careful examinations and biopsies have preceded diagnosis. Thus three of the malignancies were known at the time of treatment. While a sarcoma recurred three years after treatment and an adenocarcinoma of the uterine body was accidentally missed.

Whether radium or roentgen ray are more destructive than operative removal of tissue is questionable. If properly applied in benign bleeding uteri they are never destructive but alter the endometrium or arrest ovulation.

Electrotherapy, i.e., the Apostoli treatment cannot be compared to radiation therapy as the physical and biologic foundations of the latter differ.

DR. DANFORTH (closing).—Dr. Bauer gives the mortality in their series of vaginal hysterectomies as 1.57 per cent. The mortality in my group of operated cases was 0.28 per cent. In my early work I had some bad results with vaginal hysterectomy, chiefly due to the fact that my experience was small and that I had for a time a dislike for it. We have been using it rather freely of late years and probably will use it more in the future. Dr. Bauer brought out the fact that myomectomy is the more dangerous operation. That is one of the things which accounts for the small use that we make of it and also explains why we restricted it to a limited class of cases in which for the purpose of reproduction we wished to preserve the uterus. I think a large series of myomectomies will show a morbidity and mortality rate larger than that of subtotal hysterectomy.

Our use of irradiation is less than it was, and in another five years it will probably be less than now. Irradiation is not a conservative form of therapy, but distinctly radical and, therefore, should be restricted to cases in which the patient is approaching the menopause. Too many have been led to use irradiation and radium who are less expert in the selection of cases than Dr. Schmitz. Dr. William H. Mayo has said that the country has too many men who own a nickel's worth of radium and do a million dollars' worth of damage with it.

Dr. Gardner wanted to know about the morbidity, particularly phlebitis and embolism. I referred to one case of embolism with fatal result. We had three cases of phlebitis, all of which recovered.

I agree that vaginal hysterectomy should not be applied to large tumors and that, if irradiation has been done and bleeding occurs later, it is best to operate. I prefer to use radium in women who are well over forty.

THE NEED FOR UNIFORMITY IN REPORTING MATERNAL MORTALITY AND MORBIDITY RATES

H. J. Stander, M.D., New York, N. Y.

(From the Department of Obstetrics and Gynecology, New York Hospital and Cornell Medical College)

MATERNAL mortality in the United States has been frequently commented upon in recent medical literature, as well as in the lay press. Particular attention has been focused on the rôle played by puerperal infection in this mortality rate. Comparisons have often been made between this country and other countries. I may say at the outset that such comparisons, in my opinion, are worthless unless the same basis for computing statistics is used. If all countries and clinics adopted a method of reporting "maternal mortality rate" by stating the percentage of women, with both nonviable and viable babies, dying during pregnancy, labor and the puerperium, without correction for such complications as tuberculosis, pneumonia, heart disease, cerebral accident, anemia, thrombosis, embolism, pulmonary edema, diabetes, chorea, epilepsy, appendicitis, criminal abortion, nephritis or any other complication of pregnancy, one would be justified in making comparisons. It is the custom to speak of maternal mortality in terms of the number of mothers dying per thousand live births. This also is misleading in many instances and does not express the true state of affairs for any given locality or clinic. We are aware of the reason usually set forth for computing maternal mortality on a basis of "live births," namely, that it expresses the sacrifice in mothers to produce so many live births. This, however, leads to numerous inaccuracies and corrections. I strongly advocate a uniform method of computation and suggest that the several international and national societies concerned come to an agreement on the subject. It is my belief that all statistical studies on maternal mortality will be of slight value in the evaluation of comparative figures for different clinics, localities or countries, unless all reports are based on the total uncorrected maternal deaths, irrespective of the duration of pregnancy or the result to the offspring.

The present confusion in maternal mortality statistics is surpassed only by that existing in the morbidity figures as reported from different sources. Here, also, there is an urgent need for unification of methods of recording. The standard of the British Medical Association classifies as morbid any rise of temperature exceeding 100° F. on two of the bidaily readings after the first day to the eighth. The Strassburg standard

designates as morbid all patients with elevations of 100.4° F. or over, persisting for 12 hours or more and omitting the first day's temperature. Several hospitals have developed their own standards of morbidity.

It is evident that a bidaily temperature reading often gives very false and misleading information, especially if such temperatures are taken early in the morning and at two o'clock in the afternoon. The four or eight o'clock temperature is more significant than that at two o'clock. On such a bidaily basis of recording temperatures, many patients with an uterine infection, and even with a hectic temperature course, may appear to be afebrile. The important factor in detecting a puerperal infection is that throughout the patient's stay in the hospital her temperature be faithfully recorded at 6 and 10 A.M., 2, 6, and 10 P.M. and 4 A.M. The last temperature, 4 A.M., may be omitted if the patient is asleep. Our standard of morbidity in the Woman's Clinic of the New York Hospital is as follows: "The puerperium is considered febrile if there is a rise in temperature to 38° C. (100.4° F.) occurring once during each of two twenty-four-hour periods following delivery or remaining elevated longer than twenty-four hours, excluding the first twenty-four hours after delivery, temperatures on all patients being recorded every four hours throughout the patient's stay in the hospital."

In the matter of infections in maternity hospitals the question of adequate isolation is one of prime importance. I believe with Williams, that strict isolation technic, as practiced in the isolation wards of a medical infectious service, is adequate in an obstetric service. In the new Woman's Clinic of the New York Hospital, we planned an isolation floor on which each bed is a separate "isolation unit." All patients potentially infected or infected on admission or developing a fever of 100.4° F. on two occasions, not counting the first twenty-four hours following delivery, are transferred to this floor. The isolation floor is completely equipped with nurseries, kitchens, sterilizing room, operating and delivery room, and is subdivided into sections, one for observation and the milder forms of infection such as, pyelitis, gonorrhea, and breast infections, and one for puerperal infection. The moribidity rate in the Woman's Clinic of the New York Hospital, according to our standard as outlined above, including puerperal infection, mastitis, pyelitis, intercurrent disease, and all other causes of fever, was 10.959 per cent in 2,783 full-term and premature hospital deliveries and abortions during the year 1933. During this period the total incidence of puerperal infection, excluding mastitis, pyelitis and intercurrent disease, was 8.444 per cent. It may be of interest to note that during this same period the New York Hospital had a total of 4,387 obstetric discharges, which consisted of 3,880 full-term and premature deliveries and abortions on its indoor and outdoor services, as well as 412 patients discharged before delivery, and the remaining 95 were

patients admitted postpartum or not pregnant. The gross, *uncorrected* maternal mortality in this group was 0.159 per cent, or 1.59 per thousand patients. These deaths were seven in number and of these seven patients two died before delivery. The causes of death in these seven patients were as follows:

Acute cardiac failure	1
Pyelitis and cardiac insufficiency	1
Asphyxia, anesthetic death	1
Acute yellow atrophy	1
Septicemia with peritonitis	1
Lobar pneumonia	1
Postpartum hemorrhage	1

I cannot agree with DeLee that a separate building is necessary for adequate isolation. A floor, fully equipped, is as satisfactory as a separate building, provided the isolation technic is perfect. The technic is far more important than the separate building. Williams stated,

> "At the Johns Hopkins Hospital for nearly a generation the infectious isolation ward of the whole hospital was adjacent to the maternity ward and its entrance not 20 feet away from the door of the obstetric ward, yet serious infection rarely occurred and at no time caused anxiety. Newer and better quarters are now obtained, although the isolation ward is still nearby and the connections with the general hospital are the same." In 1927, he wrote, "It is a matter of indifference what types of patients occupy the floors above or below the maternity, so long as a really rigid aseptic technic is employed by the medical staff and the best traditions of intelligent nursing are followed."

With these statements I am in complete accord. It is the custom in many maternity clinics to record the patient's temperature two, three or four times a day, for the first three or four days, and if the temperature on these days is normal, to record it only in the morning and evening during the succeeding days. It is quite apparent that, with such a method of recording temperatures, the morbidity rate would be below that obtained if temperatures were reported every four hours throughout the patient's entire stay in the hospital. Temperatures taken twice daily, at 6 A.M. and 2 P.M., are most misleading and cannot possibly give a true index of any hospital's morbidity rate. Furthermore, puerperal infection often does not reveal itself during the first three days following delivery and will, therefore, often go unrecognized if this schedule of recording temperatures be followed.

In the matter of fetal mortality rates, as reported by different hospitals and countries, there is equal confusion. Many institutions report corrected fetal mortality rates, using different methods of correction. Such corrections may take the form of substracting all deaths where the heart could not be heard during labor, where the fetus is macerated,

where there is prematurity of some unstated degree, or where the child died some hours or days after delivery. A total infantile mortality rate, including all stillbirths in babies of 1,500 gm. or over, as well as neonatal deaths occurring during the first fourteen days of life, is the only basis on which intelligent comparisons can be made. A corrected fetal mortality rate is as misleading as a corrected maternal mortality rate.

CONCLUSIONS

1. We advocate a uniform method of reporting maternal mortality and suggest that all maternal deaths, irrespective of the duration of pregnancy or the outcome to the child, be reported in an *uncorrected* form, expressed as a percentage, and not as a ratio to the number of live births. Deaths from complications of pregnancy in the form of intercurrent disease such as pneumonia, cardiac disease, tuberculosis, and others, should not form a basis for correction.

2. We also advocate a uniform standard of morbidity, the most important feature of which is the recording of temperatures every four hours throughout the patient's stay in the hospital. We suggest that "morbidity" include all cases of puerperal infection, as well as all those febrile from other causes; and that by "puerperal infection" be meant a rise in temperature to 100.4° F. (38° C.) occurring during each of two twenty-four-hour periods following delivery, or remaining elevated longer than twenty-four hours, excluding the first twenty-four hours after delivery, unless the rise in temperature is definitely proved to be due to mastitis, pyelitis, or intercurrent infection, such as pneumonia or tuberculosis.

3. We further advocate that fetal mortality rates be reported as "total infantile mortality" by which is meant all babies weighing 1,500 gm. or over, or measuring 35 cm. or more, born dead or dying within fourteen days following birth, and that such mortality rate be reported in an absolutely *uncorrected* form.

4. We believe adequate isolation for *all* febrile patients in a maternity hospital, or in a maternity division of a general hospital, can best be obtained by isolating all potentially infected patients and all those with fever, according to the above standard, on a floor devoted *wholly* to this purpose and completely equipped to enforce strict medical isolation technic. We believe that the strict isolation technic is of far greater importance than a separate isolation building.

SYMPATHOBLASTOMAS OF THE VAGINA (2 CASES)*

MARGARET CASTEX STURGIS, M.D., F.A.C.S., PHILADELPHIA, PA.

(*From the Department of Gynecology, Woman's Medical College of Pennsylvania*)

BECAUSE of the comparative rareness of primary malignant disease of the vagina, I am reporting two cases. Both of these cases were diagnosed as sarcoma of the vagina and treated as such. Subsequent cytologic study has revealed, however, the astonishing but apparently not original suspicion that these tumors, as well as many others so reported, are of neurogenic origin and not true sarcomas.

Max Bielschowsky (Berlin) writes that tumors derived from the sympathetic nervous tissue rests, which he calls sympathogoniomas, are commonly found in the newborn and youth, and very rarely in the adult. These newgrowths he considers highly malignant. Many, he asserts, have been described as sarcomas in literature because they strongly resemble the small cell lymphosarcoma. The sympatho-, or neuroblastomas variously called, vary in cell structure from those in which immature cell types predominate to the ones in which mature cells predominate. Here, as in other tumors, experience has shown that greater malignancy corresponds generally with the greater number of immature cellular elements present.

I am indebted to Dr. Helen Ingleby for her careful study of these two tumors and her very detailed description and diagnosis. Dr. Joseph MacFarland has concurred with her in her opinion that both of these tumors are of neurogenic origin and are sympathoblastomas; the second case to be described is a very embryonic cellular type, medulla blastoma sympathogonioma.

CASE 1.—L. K., aged fifty-nine, white, was brought to me for consultation by Dr. Alice Sheppard, Pottstown, on March 7, 1932.

Bloody discharge from vagina, noticed on Dec. 25, 1931, was at first red, then became watery and blood-tinged. There was no pain, no discomfort. The discharge was noticed worse after walking and following unusual exertion.

Past history: negative. No operations, no history of cancer, tumors, etc. Patient had been married forty years. Husband living and well. Four children living and well. All normal deliveries. Menopause about ten years ago.

General physical examination was essentially negative. Blood pressure 140/70.

Vaginal examination: Vulva noninflammatory; second-degree laceration of vaginal outlet. Soft, ovoid mass about the size of a hen's egg was found projecting from the left lateral aspect of the posterior vaginal wall. This mass apparently was growing from the left side of the rectovaginal septum, about one

*Read at meeting of the Obstetrical Society of Philadelphia, January 4, 1934.

inch within the vaginal introitus. The mass was deep red in color, resilient and cystic on palpation; not painful. Cervix was seen with difficulty above the mass. It was smooth and atrophic. Uterine body palpated in anterior position, small and movable. No adnexal masses.

Rectal examination revealed a smooth, mucous membrane with a vaginal mass palpated anteriorly and to the left. There was no bulging into the rectum of this mass.

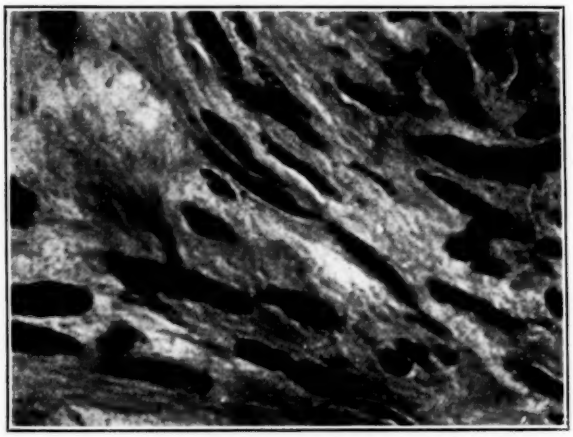


Fig. 1.—Case 1. High power.

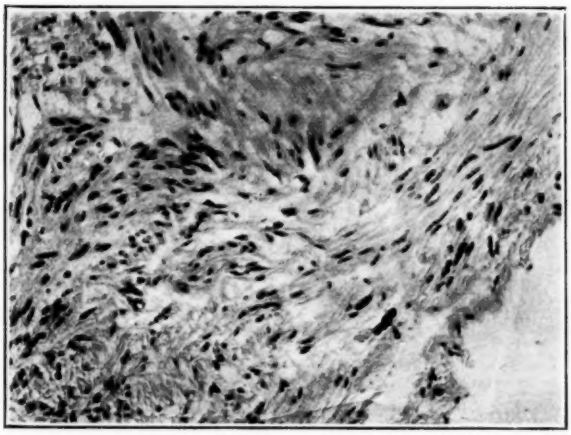


Fig. 2.—Case 1. Low power.

The clinical primary diagnosis was made of a deep-seated abscess of the recto-vaginal septum.

This mass was incised, using a scalpel, but the type of the tissue observed, the lack of resistance to the knife together with the very profuse bleeding produced by the incision led to the immediate clinical diagnosis of sarcoma and a piece of tissue was removed for examination. The bleeding necessitated packing of the vagina because this had been an office procedure and the patient would not go immediately to the hospital.

The patient was admitted to the Hospital of the Woman's Medical College, March 17, 1932. The laboratory findings at this time showed the urinalysis essen-

tially negative, Wassermann negative; sedimentation time thirty minutes; blood count: Hb. 73; R.B.C. 4,690,000; W.B.C. 15,800. Blood chemistry was normal.

On the following day 50 mg. of radium were introduced in an especially arranged cork apparatus which fitted into the vagina to hold the radium. This was allowed in for twenty-four hours. Six treatments of high voltage, deep x-ray were given on six successive days beginning April 1. The x-ray treatments were discontinued because of high temperature reaction.

Examination on April 6 showed the tumor projecting into the vagina to be larger. A slough was covering the most prominent part. The mass, however, seemed leathery and circumscribed.

On July 23, 2400 mg. hours of radium were given. Two 25 mg. capsules were inserted directly into the tumor following two puncture wounds. Three days later 2400 mg. hours of radium were again used in the same way as previously. The tumor at this time was about the size of a turkey egg and was taking on a more or less pedunculated aspect, protruding somewhat from the vaginal orifice. It was covered by a healthy grayish pink mucous membrane. There was no evidence of extension or fixation.

On Nov. 6, 1932, the patient received the final dose of 1200 mg. hours of radium into the tumor. A total of 7200 mg. hours of radium and 2670 R units of roentgen therapy had been used.

On July 20, 1933, the tumor was found to be about one-half the previous size. A firm leathery mass covered by a grayish mucous membrane entirely filled the lower part of the vagina and showed firm adhesions to the opposite walls. The vagina was contracted and the canal was obliterated. This obliteration of the vaginal canal was apparently inflammatory and not due to invasion. Rectal examination showed no evidence of invasion into the rectal wall.

Again in December, 1933, two years after first symptom was observed, the local condition had remained the same as in July. The patient is enjoying good health with no sign of extension or metastasis.

To my colleague, Dr. Faith Fetterman, I am indebted for the privilege of reporting Case 2.

CASE 2.—M. B., aged thirty-two, white, admitted to the Hospital of the Woman's Medical College June 26, 1933.

Backache and pain in vagina and rectum.

Present History: The pain in vagina and rectum, associated with headache, came on suddenly after lifting a heavy kitchen cabinet. For three weeks the patient had had pain and aching in the rectum; and between the rectum and vagina. The pain also had extended up into the back across the lower part of the spine. She was unable to sit in comfort. Had a menstrual period beginning June 22 and since then had had more relief. Patient had been using witch hazel compresses to what she thought was an abscess.

Menstrual History: Usually irregular, always more than twenty-eight days' interval. Last about two days and scanty, no dysmenorrhea, no clotting, no spotting between periods.

Marital History: Married eleven years; husband living and well. Four children living and well. Last pregnancy two years ago.

Past History: No operations, no history of cancer.

Physical Examination: Essentially negative except for enlarged and cryptic tonsils and a few palpable postcervical glands.

Pelvic Examination: Vulva noninflammatory, relaxed vaginal outlet. Vaginal walls relaxed. A tender, fluctuating mass, deeply red in color, about the size of a hen's egg, was observed bulging into the vagina from the left side.

Cervix badly lacerated. Small movable anteverted uterine body. No adnexal masses. No tenderness in fornices.

Diagnosis was made of hematoma of vaginal wall.

June 26, 1933, under nitrous oxide and ether anesthesia the mass was punctured. Since neither pus nor blood was expressed an incision was made along the vaginal wall and contents evacuated. Jellylike masses of pale yellow organized material with streaks of brownish blood were removed. It was thought at the time to be

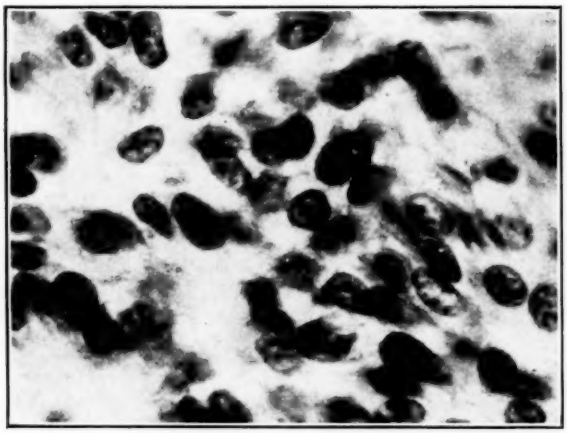


Fig. 3.—Case 2. High power.

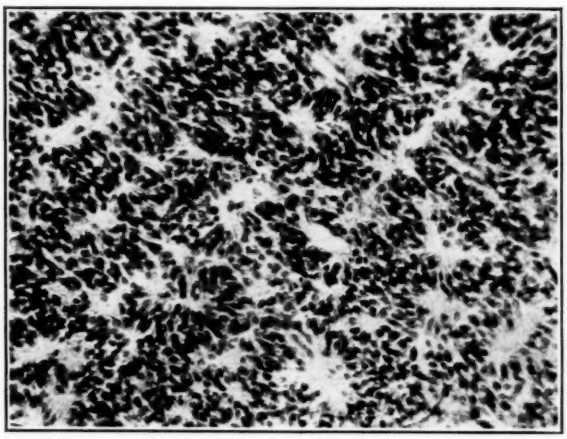


Fig. 4.—Case 2. Low power.

a "chicken jelly" clot. No free bleeding. Vaginal wall was sutured leaving inch wick of iodoform gauze packing in the depth of the cavity. The wound healed by primary union and patient left the hospital on July 1, 1933, much improved because of cessation of pain.

Roentgen therapy was commenced immediately. The patient had twelve x-ray treatments totaling 3450 R units of high voltage deep x-ray. Her last x-ray treatment was Sept. 27, 1933.

On Oct. 10, 1933, the patient was admitted to the Woman's Hospital. The growth had recurred on the left side of the vaginal wall, just inside the introitus

and was the size of an English walnut. There was no lateral bulging. At this time 6000 mg. hours of radium were given applied in six 12.5 mg. needles into the vaginal growth in one continuous application. Patient was hospitalized for one week. She stood this well with very slight febrile reaction.

On examination Dec. 26, 1933, there was no discharge but there was a return of left sacroiliac pain. There was great difficulty in defecation with ribbonlike stools. There had been a loss of 12 pounds in weight and she was growing much weaker. The size of the growth had increased and it was almost impossible to insert the finger into the vagina beyond the growth. There was also some left lateral bulging of the mass toward the rectum.

The tumor in six months showed great rapidity in growth and extension.

PATHOLOGIC DIAGNOSIS OF CASE 1

The tumor consisted of bundles of spindle cells surrounding the blood spaces. The cells were arranged mainly in bundles which run in various directions. Often bundles running at right angles to the section were surrounded by others longitudinally arranged which formed a sort of sheath around the vertical bundles. Several such bundles were surrounded in their turn by a similar sheath giving somewhat the effect of a nerve bundle. The individual cells varied a good deal. Some of the nuclei were large and plump. Others were small and spindle-shaped. Only one nucleus could be found that resembled that of a ganglion cell. Mytoses were rather frequent.

Bielschowsky's silver impregnation showed bundles of rather coarse fibrils running in various directions. Between the course of fibrils were some very fine wavy fibrils that tended to form spindles.

The structure of the tumor suggested a neurogenic origin probably sympathetic. It may have been a sympathoblastoma.

PATHOLOGIC DIAGNOSIS OF CASE 2

The tumor consisted of small spindle cells, having in most parts of the section a palisade arrangement. The nuclei tended to occur in irregular rows resembling the ribs of sand seen on the shore. A variable number of nuclei were clumped together to form these rows. Their long axis tended to be at more or less right angles to the direction of the row. Sometimes instead of rows there was a rosettelike arrangement of nuclei. In these it could be seen that the protoplasm tails off into fine fibrils which join in the center of the rosette. Wherever the protoplasm of the cells was distinctly seen, it had this fibrillary appearance. Otherwise the nuclei lay in a pale staining homogeneous matrix. The cell nuclei were sharply defined and stippled with chromatin granules. Minute nucleoli could be made out in some of them. Mitoses were fairly frequent. Thin-walled blood vessels were found throughout the section but were not especially numerous.

The tumor was undoubtedly a neuroblastoma (medulla blastoma sympathogonioma).

1930 Chestnut Street

DISCUSSION

DR. JOHN FISHER.—To my knowledge sarcoma of the vagina is a very infrequent disease. It has been found congenitally and up to eighty-three years of age. In about 75 per cent of the cases it occurs in children less than fifteen years of age. I have seen only two such cases in the practice of others.

About 1909 I examined a woman with an enlargement, about the size of a walnut, of the anterior vaginal wall, that extended up the right lateral fornix. The uterus was not involved and at that time we knew nothing about the use of radium. There was such an extensive involvement of the anterior vaginal wall that we thought it more risk to remove the growth. A section was taken and the macroscopic diagnosis of adenocarcinoma was made with the idea in mind that it had originated in an unobliterated portion of Gärtner's duct. Subsequently a suburethral growth was removed. The diagnosis of adenocarcinoma was not proved microscopically.

DR. STEPHEN E. TRACY.—We have had three cases of sarcoma of the vagina. The first was a woman fifty-three years of age. Examination revealed a mass about 6 cm. in size at the right side between the vagina and the rectum. The entire mass was removed at operation. The patient did well for a short time, but died about two and one-half years after discovery of the growth.

In the second case the growth was 3 cm. in diameter and was located in the vesicovaginal septum. The mass was removed at operation. The patient left about two months later and could not be located. It is only fair to assume that she died from a recurrence at a later date.

The third patient was a single woman thirty years of age. Examination showed a mass 8 cm. in diameter, situated on the right side beneath the vaginal wall. The clinical diagnosis was sarcoma of the vagina. The mass was removed and the pathologist reported the tumor was degenerated fibroid tissue. Several pathologists concurred in the diagnosis. About nine months later the patient returned. At that time, there was a mass in the same region 50 per cent larger than the original growth and this was removed at operation. The bleeding was profuse and could be controlled only by packing the cavity tightly with gauze. Ten days later the wound was opened and 100 mg. of radium filtered with 1 mm. of brass and 1 mm. of rubber was placed deep down in the tissues and allowed to remain twenty-four hours. There was a marked general reaction following the application of the radium. Later a rectovaginal fistula developed which healed in a few months. The patient is living with no evidence of recurrence at this date, January, 1934.

We had another patient with a growth at the right side of the vagina which was diagnosed clinically as a sarcoma. The mass was removed and the pathologist confirmed the clinical diagnosis. However, another pathologist went over the slides last week and decided the tissue was carcinomatous and not sarcomatous.

That the patient lived only two and one-half years after the tumor was discovered, is a certainty

FURTHER OBSERVATIONS ON THE EFFECT OF FEMALE SEX HORMONE UPON THE BLOOD OF NEWBORNS*

JOHN C. HIRST, A.B., M.D., F.A.C.S., PHILADELPHIA, PA.

IN A previous study[1] of normal newborn infants we showed that injections of theelin moderately reduced blood coagulation and bleeding time in both sexes, as well as in male bleeders. It was also suggested that breast engorgement was probably increased, icterus neonatorum modified, and vaginal bleeding initiated by these injections, to be verified by further study.

The present report, therefore, includes additional observations on these points, but mainly on the effect of larger doses of theelin upon hemoglobin, red and white blood cells, and particularly blood platelets. Estimations of platelet fragility were also attempted, but discarded because of the amount of blood required, and too wide variation in results. The charts (Charts 1 to 4) were compiled from figures obtained over a period of two months by an expert full-time technician from series

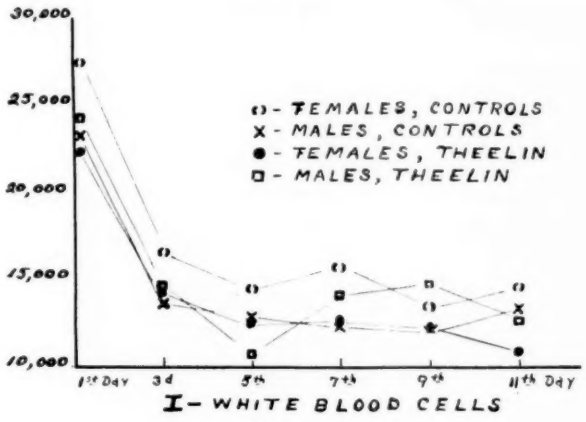


Chart 1.

of consecutive newborn infants in the Department of Obstetrics, Hospital of the University of Pennsylvania, through the courtesy of Professor E. B. Piper.

Eighty-six newborn infants were studied for a minimum period of twelve days under identical conditions, approximately one-half as controls and one-half as subjects of daily intramuscular injections of pure "theelin," generously provided by Parke Davis and Company in ampules of 50 rat units per cubic centimeter solution. The injections were begun after the fifth day, i.e. after presumable excretion of maternal estrin, and continued until discharged from the hospital, so that the treated infants received at least 300 R. U. of female sex hormone. Based upon a weight ratio of 1:20, this dosage is greatly in excess of the amount found by me[2] to produce certain female sex hormone manifestions in adults, and more than twice as much as the minimum dosage found by Werner and Collier[3] to produce endometrial proliferation in castrated women.

RESULTS

Analyses of our observations are considered under four groups:

Group I.—Male Controls (21): The most significant feature is the rapid rise of blood platelets, indicating either a disproportionate elaboration of platelets, or more

*Read at meeting of the Obstetrical Society of Philadelphia, January 4, 1934.

probably decreased fragility. Differential white blood cell counts of 8 babies showed generally low proportion of leucocytes, high lymphocytes, and many eosinophiles, particularly after theelin injections. Estimations of bleeding and coagulation times from 15 patients showed the former averaging under three minutes, none over seven and one-half minutes. Of the latter, averaging under six minutes, one gave the interesting figures shown in Table I.

TABLE I

DATE	COAG. TIME	BLEEDING TIME	PLATELETS	REMARKS
3-14-33	5 min. 10 sec.	1 min. 45 sec.	261,000	No
3-16-33	2 min. 0 sec.	1 min. 30 sec.	166,000	other
3-18-33	10 min. 15 sec.	3 min. 30 sec.	194,000	unusual
3-21-33	11 min. 0 sec.	2 min. 30 sec.	389,000	features
3-23-33	10 min. 30 sec.	2 min. 30 sec.	456,000	
3-25-33	18 min. 0 sec.	7 min. 15 sec.	578,000	

Twenty of this group were breast fed, 2 with complementary formulas, and discharged in good condition. One of premature twins, wholly bottle fed, died on the eleventh day. Most of these male controls were circumcised, without undue bleed-

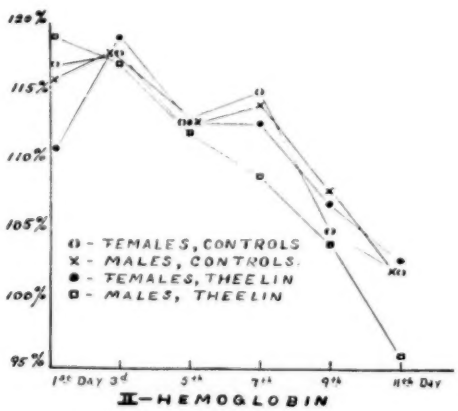


Chart 2.

ing, and there were no additional significant items other than one instance of generalized eczema. Breast engorgement was not noticeably frequent or severe.

Group II.—Female Controls (21): The platelet curve rises almost as sharply as that of the male controls, which indicates that both male and female newborns develop decreased platelet fragility as a result of excretion of maternal and placental estrin after birth. As in each group, although the charted platelet figures were obtained by the older method of counting, 88 total check counts were made by the newer staining method, giving $\times 2.3$ proportionately higher results, more closely representing actual figures. Likewise, differential white blood cell counts in 9 infants approximated those of the male control group. Bleeding and coagulation times from 15 newborns showed very short averages, less than two and one-half minutes for the former, less than six minutes for the latter, and no extremes in either case.

Two infants had complementary and 3 entirely bottle feeding, and all were discharged in good condition. Only one infant showed marked icterus, and none developed bleeding from the vagina. Engorgement of the breasts was average in amount and degree.

Group III.—Male Newborns Treated with Theelin (25): The platelet curve is definitely lower than that of the untreated male infants, indicating increased fragility of the platelets. One male bottle-fed, premature newborn (second of twins, first died, q.v.) received 1 c.c. (50 R.U.) of "theelin" daily for sixteen days (total 800 R.U.) with no untoward results, but probably as the result of repeated glucose administration[4] the red blood cells dropped from 5,300,000 at birth to 4,100,000 at twenty-second day, platelets from 273,000 to 175,000, coagulation time from four minutes to two minutes fifteen seconds, hemoglobin from 110 per cent to 80 per cent. Differential white cell counts of 12 infants showed even lower leucocytic, higher

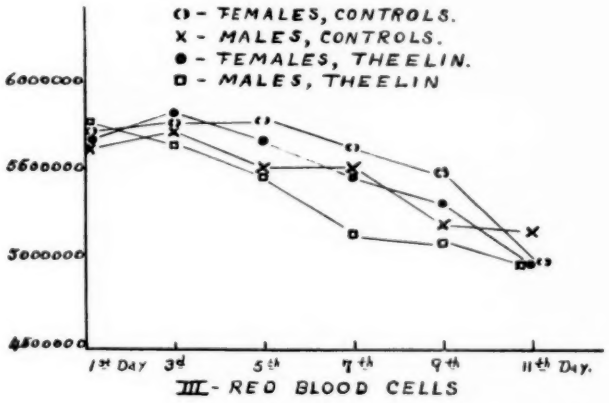


Chart 3.

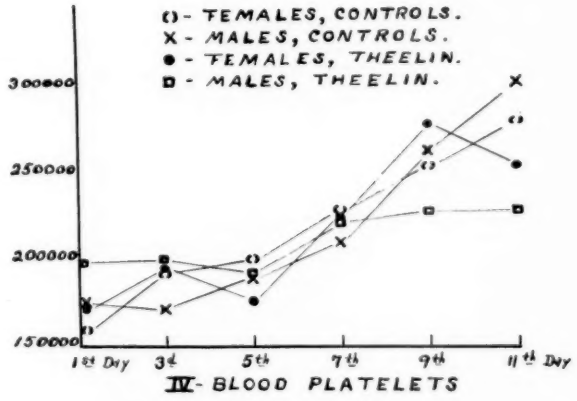


Chart 4.

lymphocytic and more decided eosinophilia than the same tendency noted in the two control groups. Bleeding and coagulation times of 20 cases were slightly less than the male control group, averaging less than two and one-fourth and four and one-half minutes, respectively.

Twenty-one of this group were breast fed, 2 complementary, 2 bottle fed, and all were discharged in good condition. Most were circumcised, without complication, but one with early hemorrhage from loose ligature. Other special features were as follows:

One urticarial rash began fourth day, disappeared after the second theelin injection.

Four cases of jaundice, three before injections were begun, one very severe, persisting at discharge on the fourteenth day.

One infant bled freely at the second, third, and fourth injections, and after the third, fourth, and fifth heel puncture, in spite of all normal test readings.

Breast engorgement was not common in this group, but not noticeably altered after appearance.

Group IV.—Female Newborns Treated with Theelin (19): The platelet curve is also lower than that of the female controls, indicating that both male *and* female newborn infants are similarly affected by administration of theelin. This is a natural result, since both sexes eliminate equal quantities of maternal and placental estrin, and therefore should be similarly affected in the first few days of life. From this and from our prior finding of decreased coagulation times by injections of theelin, it may be concluded that there is a predisposition to hemorrhagic disease in newborns of each sex (although in different manner and degree). One infant received 20 c.c. of theelin, 50 R.U. each (total 1,000 R.U.), from the seventh to the twenty-eighth day without any untoward effect, only moderate drop of blood platelets, but some *increase* in coagulation time. Differential white cell counts from 9 of this group again showed preponderance of lymphocytes over leucocytes, and many eosinophiles. Bleeding and coagulation times in 14 infants again yielded very short readings for the former, with nearly the same coagulation times as in the normal female control group. Only one of this group was bottle fed, one complementary feeding and all were discharged in good condition.

The following special features were noted:

One case of decided jaundice from the sixth to the fourteenth day (discharged), not affected by theelin.

One case of urticaria began eighth day, persisted until discharge.

One case of bright vaginal bleeding, began fifth day (before theelin), profuse through tenth day, and absent during last three days of injection. Nothing significant in any of the blood studies of this infant, which indicates entirely functional nature, i.e. withdrawal (elimination) of maternal-placental estrin as the usual cause of uterine bleeding in newborn females. Administration (substitution) of theelin, therefore, can be expected to cause cessation of this type of uterine bleeding, as well as the hemorrhagic type, or in some cases to initiate uterine bleeding as in castrates.

Breast engorgement was not distinctly affected in this group, although not frequent.

SUMMARY AND CONCLUSIONS

1. Eighty-six newborn infants were studied to ascertain the general effect of daily 50 rat unit intramuscular injections of theelin after the fifth day, as well as the effect upon hemoglobin, red and white blood cells, and especially blood platelets.

2. The natural rise of blood platelets in males and females was retarded, indicating the production of increased platelet fragility by administration of theelin. The natural fall of hemoglobin, with red and white blood cells was not affected.

3. No harmful effects were noted even in prolonged usage of theelin, up to 1,000 R.U.

4. Icterus neonatorum ("physiologic type") was not affected by theelin.

5. Theelin causes cessation of functional (or hemorrhagic), vaginal (uterine) bleeding even though it may initiate hormonal bleeding.

6. Engorgement of the breasts was not common, but not affected when present, suggesting that earlier administration is required to prevent lactation in the newborn.

7. Newborn infants of both sexes are subject to hemorrhagic disease of the newborn by increased fragility of their blood platelets from elimination of maternal-placental estrin after birth. Therefore as an adjunct to transfusion, intramuscular injections of theelin should be useful in any instance of neonatal hemorrhagic disease.

REFERENCES

(1) *Hirst, J. C.:* Am. J. Obst. & Gynec. **26:** 217, 1933. (2) *Hirst, J. C.:* Am. J. Obst. & Gynec. **15:** 487, 1928. (3) *Werner, A. A., and Collier, W. D.:* J. A. M. A. **101:** 1466, 1933. (4) *Mitchell, J. McK.:* Am. J. Dis. Child. **38:** 518, 1929.

1918 Pine Street

CHORIONEPITHELIOMA OF THE UTERUS*

Thomas C. Peightal, M.D., New York, N. Y.

(From the Gynecological Service of The Roosevelt Hospital)

THE following case is reported chiefly to emphasize the favorable reaction of chorionepithelioma to radium and x-ray:

N. A., aged twenty-nine, was married three and one-half years, with a history of 4 pregnancies. Two were spontaneous miscarriages, the first three years previously at two months and the second two years and eight months before at four months. Two were normal full-term deliveries, the first one year and seven months and the second seven months before her recent illness.

This patient was admitted Oct. 31, 1932, to the Roosevelt Hospital complaining of pains in left back and flank, dysuria, hematuria, and chills of three days' duration together with varying degrees of metrorrhagia which had persisted since the birth of her last child seven months previously. This almost continuous moderate metrorrhagia showed periodic monthly increase for five or six days corresponding to the expected time for her menstruation. On admission the uterine bleeding was of slight degree while the hematuria was of such severity that the urine contained gross blood and clots sufficient to cause marked dysuria from their passage.

On general physical examination the patient was anemic (hemoglobin 50 per cent, R.B.C. 2,940,000; W.B.C. 8,850; polymorphonuclears 73 per cent) blood pressure 128/68, and the heart and lungs normal to auscultation and x-ray. There was marked tenderness over the left kidney and cystoscopic examination revealed brisk hemorrhage from the left ureteral orifice and a filling defect in the pyelogram. The uterus was very slightly over average size, soft and freely movable without pain, and there was a scanty bloody discharge through a patulous cervix. The broad ligaments and adnexa were normal. The vaginal walls were relaxed but otherwise normal. Blood chemistry was normal and blood culture and Wassermann negative. Aschheim-Zondek test was done on the bloody urine but unfortunately all the mice died.

A diagnostic curettage was advised but because of the severity of the kidney hemorrhage and the likelihood of kidney tumor it was decided that nephrectomy

*Read at a meeting of the New York Obstetrical Society, Dec. 12, 1933.

should be done first. After two indirect blood transfusions of 400 c.c. each the left kidney was removed November 14. A tumor was found 3 cm. in diameter, extending from the surface down to the kidney pelvis and surrounded by a large area of hemorrhage.

Microscopically the kidney tissue was invaded by masses of large loosely joined cells containing irregular, ovoid hyperchromatic nuclei and other cytoplasmic masses of large branching acidophilic cells which contained numerous dark staining nuclei clustered together. A diagnosis of mixed tumor of the kidney (Wilms) was made at this time.

Two weeks later, November 28, after a normal convalescence, the uterus was explored by curettage. The fundus was one and one-half times average size and the adnexa were normal to palpation under general anesthesia. At this time was noted on the anterior vaginal wall 1 cm. from the urethral meatus a dark blue tumor mass, 1 cm. in diameter which had not been present three weeks previously. This was excised. From the cavity of the uterus was curetted about 25 c.c. of what

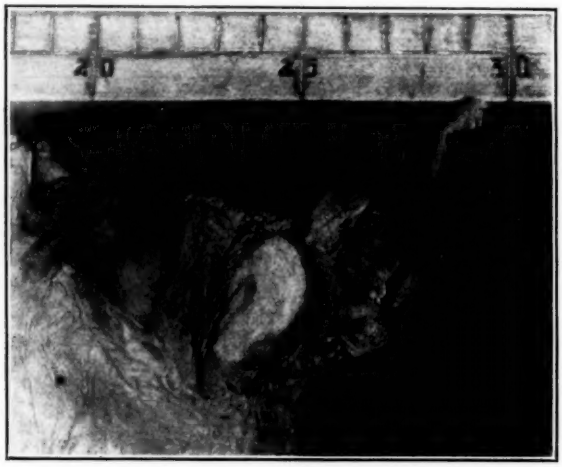


Fig. 1.—Autopsy specimen, four months after irradiation, showing marked regression of the uterus. Compare its size to that of the ovary.

grossly appeared to be dark necrotic placental tissue quite densely adherent to the uterine wall. There was only moderate hemorrhage.

Pathologic examination of the curettings, the tumor removed from the vaginal wall, and a review of the kidney tumor revealed that these three growths were identical. Also, since the two cellular elements described above were both syncytial and Langhans' cells in invading masses without evidence of connective tissue stroma or villus formation, this was without a doubt a chorionepithelioma or choriocarcinoma, primary in the uterus and metastasizing to the kidney and vaginal wall.

Five days after the curettage a third indirect blood transfusion of 400 c.c. was given. At this time x-ray of the skull, spine, pelvis, and femora revealed no bony lesion and x-ray of the lungs was again negative for metastases. The Aschheim-Zondek test, however, was strongly positive.

Because of the likelihood that other metastases already were present, it was decided to treat the growth locally in the uterus with high voltage roentgen and radium therapy rather than by hysterectomy. Ten days after curettage (December 6) high voltage therapy was begun through two anterior and two posterior pelvic portals giving 335 R units through one of these portals each day for eight successive days, each portal thus receiving two exposures in this time. Two days after

the last x-ray treatment the uterine cavity received 1800 mg. hr. radiation with radium element in 0.5 mm. platinum filtration.

At this time (December 21) the patient was in good general condition. Hemoglobin 63 per cent and R.B.C. 3,000,000 with no evidence of local spread of the growth in the pelvis and no lung symptoms. The Aschheim-Zondek test was still strongly positive in 1:10 dilution, weakly positive in 1:25 and negative in 1:50 dilution. However, the roentgenogram now for the first time showed multiple metastases, from 1 to 2 cm. in diameter in the periphery of both lungs. In spite of this during the next month the patient continued to improve generally and the lungs by x-ray showed some evidence of a spontaneous decrease in the size of the metastases, while the uterus was reduced to less than half its original size. A fourth indirect blood transfusion of 400 c.c. was given. The Aschheim-Zondek test was now only weakly positive with undiluted urine.

On Feb. 6, 1933, two months after the first high-voltage therapy, a second pelvic cycle was given, similar to the first of 335 R units for eight successive days, and

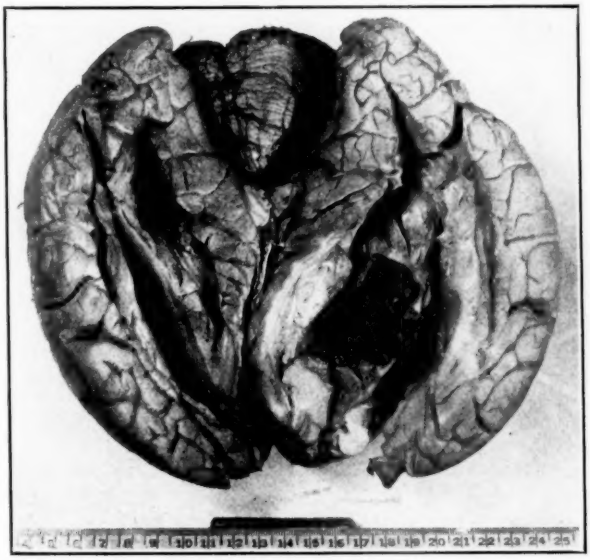


Fig. 2.—Brain, showing size and location of the metastatic lesion which caused death.

following this the chest received two high-voltage treatments of 335 R units each. Roentgenograms two weeks later showed no x-ray evidence of metastases in the lung parenchyma. The Aschheim-Zondek test was still only faintly positive with undiluted urine. The patient was allowed to go home and was able to attend to many of her household duties.

The patient was then examined on recall in two weeks and again three weeks later on March 30, 1933. Her general condition was good, the uterus was very small, only about 6 cm. in length, and there was no evidence of additional vaginal or pelvic metastases. The Aschheim-Zondek test was now more strongly positive with undiluted urine but negative in 1:10 dilution.

One week later, April 6, 1933, the patient was brought to the hospital vomiting, semiconscious, and evidently having just had a cerebral hemorrhage, resulting in a right hemiplegia. X-ray of the chest showed no further evidence of metastases. Death occurred in thirty-six hours.

At autopsy a loosely organized tumor mass, 5 cm. in diameter, was found in the wall of the left ventricle of the brain surrounded by considerable hemorrhage, with

blood in the third and fourth ventricles also. The lungs were normal except for five small nodules of regressing tumor tissue, the largest being only 1 cm. in diameter. The uterus measured 7 by 5 by 3 cm. and the endometrial cavity was almost obliterated, being lined by a thin membrane of opaque yellow material, typical of radiation necrosis. The vaginal walls, adnexa, and parametria showed no evidence of metastases. The other organs were normal.

Microscopically the tumor tissue from the brain and lungs was identical with that found previously in the uterine curettings. The uterine tissue showed marked hyaline degeneration with many fibroblasts, phagocytes, and lymphocytes and rarely a few small scattered strands of syncytial cells imbedded in necrotic hyalinized tissue. Thus both anatomically and histologically those portions of the growth which had received radiation showed marked degeneration and regression.

Several conclusions may be drawn in discussion of this case.

The x-ray may give a somewhat false impression as to the amount of regression in lung metastases. In this case the films showed a marked regression and finally disappearance of the metastatic lung shadows but at autopsy small areas of tumor tissue were still present in the parenchyma. The decrease in the size of these shadows can be explained by the fact that sizable areas of hemorrhage and consolidation, occurring around the pulmonary metastases when they are first implanted, project an image on the roentgenogram which rapidly diminishes in size as the hemorrhage is absorbed. Thus the true regression of the tumor tissue itself cannot accurately be estimated.

The value of the Aschheim-Zondek test in this case seems to be quite definite. The positive reaction became much less pronounced as regression occurred and later when the brain metastasis developed a positive test was obtained in dilutions which had previously become negative. If proper laboratory facilities are available a periodic quantitative estimation of prolan in mouse units per liter of the patient's urine would be definitely valuable not only in indicating regression but also in detecting the presence of metastases before they become clinically discernible.

The value of radiation therapy has been confirmed. One is greatly impressed with the marked favorable reaction of this choriocarcinoma to treatment with the high-voltage roentgen ray and radium. It seems to me that, without the cerebral metastasis, this growth had been brought under sufficient control to greatly prolong the patient's life; and that, except for this unfortunate accident, a cure such as is reportd occasionally in the literature might have resulted.

Estimation of the best course of therapy is difficult since each case presents individual problems which must be met as they arise. In retrospect one wonders, had this patient's condition permitted of hysterectomy at once, whether there would not have been less chance of her developing lung and brain metastases. In adenocarcinoma of the fundus we feel that the use of high-voltage roentgen and radiation therapy *before* hysterectomy offers the best chance for a cure. But in choriocarcinoma another factor makes the value of such a course of procedure doubtful. It is well known that the slightest trauma to the uterine growth may dislodge metastases into the blood stream. These cases are nearly always diagnosed by curettage. If radium and high-voltage therapy is then used before removal of the uterus the value of such therapy in decreasing the likelihood of local pelvic recurrence after hysterectomy is more than offset by the increased chance of metastases being thrown off during the necessary time elapsing between curettage and hysterectomy while the radiation therapy is being carried out. From a perusal of case reports in the literature and from the experience of this case I feel that, when possible, immediate hysterectomy followed by intensive high-voltage roentgen therapy offers the best possibility for a cure.

106 East Seventy-ninth Street

AVERTIN IN GYNECOLOGY*

RICHARD B. SCHUTZ, M.D., KANSAS CITY, MO.

(From the Gynecological Service of Kensington Hospital for Women.)

THIS report covers 353 cases at the Kensington Hospital for Women, and includes all the usual gynecologic operations, as well as one bowel resection for annular carcinoma of the hepatic flexure, two cholecystectomies, and four radical breast amputations. Vaginal operations comprised 22.6 per cent of the total, abdominal sections alone, 66 per cent plus and combined vaginal and abdominal operations, 10.2 per cent.

Table I indicates the distribution of cases as to types, indicating the number of each type in which gas and ether were used as accessory anesthetics.

TABLE I. THE USE OF AVERTIN IN 353 GYNECOLOGIC CASES

TYPE OF OPERATION	AVERTIN ALONE	AVERTIN AND GAS	AVERTIN, GAS, ETHER
Abdominal section	73	151	9
Plastic and section	16	19	1
D. and C., and plastics	38	31	0
Breast amputation	4	0	0
D. and C. including therapeutic abortion	8	3	0
	139 (39.3%)	204 (57.7%)	10 (3.0%)

It is the consensus of opinion that to insure complete anesthesia in all cases requires a dosage too large to be safe. Though Peterson and Pierce used 110 mg. per kilogram of body weight with excellent results, many have used 80 to 90 mg. hoping to insure the maximum safety and have been disappointed in the results, reporting restlessness of the patient and the use of larger amounts of nitrous oxide or ether than had been anticipated. In this series the 100 mg. dosage was employed in the vast majority of instances, providing the total amount of avertin to be used did not exceed 7 c.c., which is the dosage for a patient weighing 155 pounds. Thus, in the case of patients weighing more than 155 pounds, 7 c.c. was the maximum dose. In a few cases where obesity was extreme, cachexia or anemia marked, the 90 mg. dose was employed.

The following figures may give a more lucid idea of the amount of accessory anesthetic required, and we hope to demonstrate that though the aim is only to procure basal anesthesia, by careful management, the

*Presented by Dr. Z. B. Newton at meeting of the Obstetrical Society of Philadelphia, Jan. 4, 1934.

result is often a very successful general anesthesia. The average operating time in this series was forty-two minutes per operation. Of this time gas was administered during 24.3 per cent of the operating time. In cases where gas was used, which often represent the longer cases, gas was given 45.5 per cent of the time. A mixture of 40 to 50 per cent nitrous oxide and oxygen is all that is required, which amount if administered alone would produce only a mild analgesia. Ether administration represented only 0.70 per cent of the operating time.

Of all cases reported, 39.3 per cent required no gas at all, which figure includes all of the breast amputations, 56.6 per cent of the plastic operations, 28.5 per cent of the abdominal sections, and 16.6 per cent of the cases listed as plastic and section. In the group of sections requiring no gas were one cholecystectomy and the one bowel resection. The low percentage of plastic and section operations not requiring gas is to be expected due to the greater average length of operation and the disturbance of the patient incident to the necessary movement in changing the operating position.

The reasons found for requiring gas in addition to avertin are as follows: for making the skin incision, occasionally, when enough time had not elapsed between the administration of the avertin and the beginning of the operation; packing off the bowel; unusually vigorous traction on pelvic structures, or in freeing dense adhesions; insertion of skin clips, and insertion of the deep sutures in posterior colporrhaphies.

One point that should be emphasized, is that if a patient stirs and seems about to awaken during an operation, due to some particular manipulation, and gas is administered, it does not signify that the gas must be continued. Certain painful stimuli rise above the pain threshold only as long as the stimuli persist. With the cessation of the irritating procedure the gas may be discontinued and the avertin anesthesia persists as before. Observant cooperation between surgeon and anesthetist is essential if the amount of gas administered is to be reduced to the minimum.

It may be added that highly nervous patients, those in pain at the time of operation, children, and very young adults possess a much higher tolerance for avertin and dosages of from 105 to 110 mg. must be given for the best results. It is of great advantage if the person calculating the dosage has had the opportunity to see and talk to the patient before deciding on the amount to be used. Each dose should be individualized for the best results.

ADMINISTRATION AND CLINICAL COURSE OF THE ANESTHESIA

After varying the technic several times in the first 40 cases, the following has been adopted. The bowel is prepared by a soapsuds enema the night before operation, and is repeated early the next morning. Phenobarbital, gr. iii, is given by mouth the night before, and seems to be a most valuable preoperative procedure.

An hour before the operation is scheduled, hypodermic injections of morphine sulphate, gr. ¼, and atropine sulphate, gr. 1/150, are administered. The avertin solution is prepared on the floor where the patient is located. A 4 per cent solution of avertin fluid is prepared in distilled water at 104° F. and given immediately, after thoroughly mixing and testing a sample with Congo red for the presence of normal alkalinity. We have never encountered the acid reaction. In the patient's room, thirty minutes before the operation is scheduled, the solution is given slowly by funnel and catheter into the lower bowel. Absorption is slower in the lower bowel and the likelihood, therefore, of sudden fluctuation of blood pressure is avoided. The patient is immediately catheterized and sent to the operating room where she is attended by a nurse until time for the operation.

Within the first five minutes after the administration of the anesthetic, the patient is usually in a deep sleep, often snoring, the features usually tinged with a very slight cyanosis, but the pulse and respiration are but slightly changed. The pulse is usually slow and strong, and on the whole both pulse and respiration resemble the normal rhythm, excitement and nervousness at the approach to the operating room being wholly eliminated. Patients rarely remember more than being wheeled from their rooms, and we have not had a single patient who remembered the waiting or operating room.

The operation then proceeding with the use of nitrous oxide if necessary, the patient is watched for the possible accident of swallowing the tongue, since the cough reflex is abolished under avertin anesthesia. Stimulants have been given to four patients in this series. Caffeine sodium benzoate, gr. 7½, was given for respiratory depression. The response was rapid and no further stimulation was required. In one instance a patient seemed to be suffering sudden shock early in the course of a breast amputation, exhibiting pallor, clammy skin and fast pulse. One cubic centimeter of ephedrine produced a normal status in about a minute, and the operation proceeded uneventfully.

During the operation the absence of visible perspiration on the patient's skin has been noted. Thus about 1,000 c.c. of fluid is retained in the tissues that would have been lost with ether anesthesia. We feel that this avoidance of fluid loss by excessive perspiration is an important factor in avoiding shock and postoperative pneumonia precipitated by accidental exposure of the moist skin.

After being returned to bed the patient is watched carefully for swallowing of the tongue. This accident occurred once in this series, and only momentarily. Awakening is quiet as from a normal sleep with no tossing about, restlessness, or mental confusion. The average length of sleep is four and one-fourth hours, 18 per cent of patients slept five hours or over and 12 per cent two hours or less. The longest period was six hours and the shortest one and one-half hours.

The criterion of the stage in which a patient need not be watched for respiratory accidents is the first moan or spoken word, which indicates the return to function of the pharyngeal and laryngeal reflexes. The patient usually drops off into a normal sleep shortly after awakening and morphine is often not required until midnight.

In this series, 2.2 per cent of the patients vomited on recovering from the anesthetic. The heretofore ever-present emesis basin has practically disappeared from the head of the beds in the ward. Certainly this decrease in vomiting, with its concomitant tendency to dehydration, as well as sparing the patient the pangs of vigorous abdominal exercise immediately after operation, is a potent factor in the production of smooth convalescence. It is one of the advantages for which the patients are most grateful.

We feel that the absence of vomiting and the early administration of fluids permitted by this situation are important factors in the observed reduction of abdominal distention.

In this series five deaths occurred, showing an incidence of 1.4 per cent, only one of which could have been contributed to by the use of avertin. One patient died of embolism on the sixth postoperative day after a normal convalescence. One died of bladder necrosis forty days postoperative. One of cardiorenal disease six days postoperative. One other died of peritonitis on the sixth postoperative day, and one of uremia on the sixteenth day postoperative. This last patient was a poor risk for operation. The clinical picture was that of uremic coma. We cannot prove or disprove the part avertin played in the etiology of the renal collapse, especially as the terminal condition followed nitrous oxide anesthesia twice in one afternoon.

One other renal complication occurred in a patient who certainly should not have had a general anesthetic at all, as we see it in retrospect. This patient had a cystocele repair in an attempt to improve the drainage of a bladder desperately distorted and atonic, as a result of long-standing purulent chronic cystitis. The patient developed uremia with coma from which she recovered completely.

We have encountered no case of postoperative pneumonia. Three patients were operated upon in the presence of subacute bronchitis but no exacerbation was produced.

No cases of rectal irritation were encountered, nor was there any marked fall of blood pressure.

201 Plaza Theater Building

DISCUSSION

DR. WILLIAM E. PARKE.—Our experience with avertin in 5 or 6 obstetric cases has led us to abandon its use as a routine practice. The dose, 70 to 80 mg. per kilo, is less than that given for complete anesthesia. Consequently the patient sleeps between pains, but when a pain comes on she wakes up and becomes so uncontrollable that it takes one or two nurses to hold her on the table. Moreover the administration of the drug requires more skill and trouble in the matter of getting the drug into the bowel and keeping it there when a pain comes on than other methods of analgesia.

I have employed it in conjunction with gas for a cesarean operation with great satisfaction, and without notable effect on the baby.

For gynecologic work, supplemented if need be with gas and occasionally ether, we have found avertin to be a most satisfying anesthetic. The high spots to be emphasized after safety are the absence of *psychic shock*, and *amnesia*.

THE SEASONAL TREND IN THE CONCEPTION OF MALFORMATIONS

WILLIAM F. PETERSEN, M.D., CHICAGO, ILL.

(Department of Pathology and Bacteriology, University of Illinois College of Medicine)

IN A PREVIOUS paper* I presented some of the evidence that malformations are regionally distributed in America, increasing in the regions of greatest autonomic demand. Both the mortality statistics of the registration area as well as the results of the Draft examination revealed a distinct accentuation along the line of the storm tracks.

In the Hippocratic text one finds repeated statements that there occurs "corruption in the coagulation of the seed" with storms, in more modern terms, an interference with the normal development of the embryo.

In view of the fact that I have been able to determine the wide variations in the vascular mechanism, in the oxidation-reduction potential, in all the chemical balances when determinations are made day by day in the normal, as well as in the sick, individual and since these rhythms are conditioned by the meteorologic alterations, it seemed logical to assume that in particularly unstable individuals or with unusually severe meteorologic alterations, the uterine environment, too, might be subject to rapid and marked alterations so that an embryo in its earliest segmental stages might be subjected to an environment that could readily lead to malformations. The more so since we are aware of the marked effects of alterations of P_H, K:Ca ratio, transient periods of anoxemia, etc., in the experimental production of malformations.

With this in mind, I have collected data on the presumptive months of conception of malformed infants in a group of Chicago hospitals (Presbyterian Hospital, Grant Hospital, Children's Memorial Hospital, Michael Reese Hospital, and the Research and Educational Hospital). The total number of cases found was 403. The individual types are evident in Chart 1, Graphs A, B, and C. In A and B there are included the more severe malformations, C includes the malformations of the extremities.

The percentage monthly distribution of conceptions of normal infants delivered in the same hospitals during this time is indicated in the solid line of Graph D while the percentage distribution of the malformed infants is indicated in the double line of the same graph.

*AM. J. OBST. & GYNEC. 28: 70, 1934.

When we now relate these observations to each other, i.e., when we calculate the actual conception of the malformed on the basis of what the normal expectancy would be for each month we obtain the curve E. This would indicate that in this region (Chicago) there are distinctly more conceptions of malformed infants in the months of March and

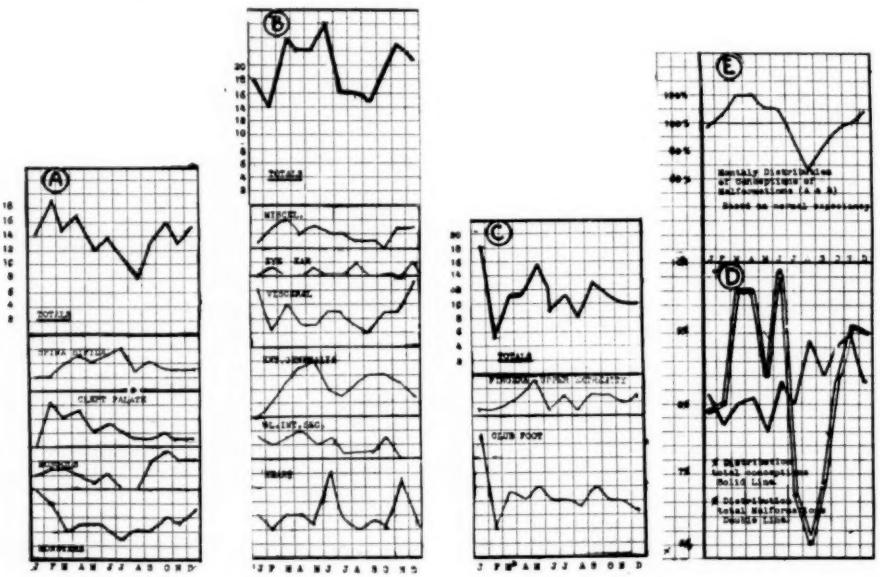


Chart 1.—*A*, Spina bifida, cleft palate, Mongols, monsters. *B*, Miscellaneous, eye and ear, visceral, external genitalia, sl. int. sec., heart. *C*, Finger and upper extremity, clubfoot. *D*, Percentage of distribution of total conceptions, solid line; percentage of distribution of total malformations, double line. *E*, Monthly distribution of conceptions of malformations (*A* and *B*) based on normal expectancy.

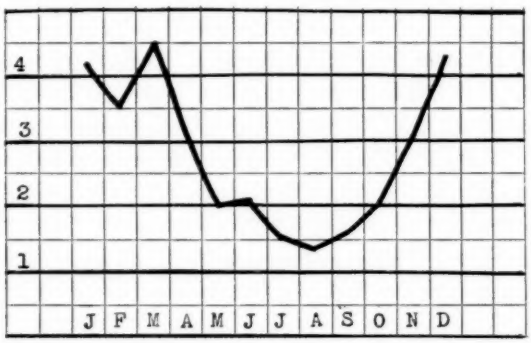


Chart 2.—Index of barometric variability in Chicago.

April (120 per cent of the expectancy) as contrasted to the small number conceived during the months of July, August, and September.

The reason for this is to be sought in differences in meteorologic stability and instability and its reflection in the autonomic balance of the maternal organism.

In the spring the protoplasm is distinctly unstable. The organism is exhausted, more acid, and the cells are more permeable and more irri-

table. In the fall the cells are less irritable and less permeable, the organism is more stable, the buffering more adequate. Consequently the probabilities for interference with normal cell growth will be greater in the spring than in the fall.

We can express the meteorologic instability if we measure the variability of the barometric pressure month by month. For Chicago the monthly index is in the following order: January, 0.420; February, 0.350; March, 0.450; April, 0.307; May, 0.201; June, 0.217; July, 0.154; August, 0.139; September, 0.168; October, 0.201; November, 0.312; December, 0.433.

This is graphically shown in the small chart (Chart 2) in which the averages for from 1915 to 1932 are shown. It makes evident the marked differences that exist in the meteorologic turbulence between the spring and late summer seasons.

I assume, of course, that the more severe malformations will be due to disturbances in the earliest stages of segmentation. On the other hand malformations of the extremities may occur later and in many instances from purely adventitious causes. Whether or not this can be substantiated I do not know.

THE TREATMENT OF GONORRHEA OF THE CERVIX

SCOTT D. BRECKINRIDGE, M.D., F.A.C.S., AND A. J. WHITEHOUSE, A.B., M.D., LEXINGTON, KY.

(From St. Joseph's Hospital, Public Health Center Clinics, and City Venereal Disease Clinic)

GONORRHEAL infection in the female is characterized by its chronicity and resistance to treatment. This may be explained, at least in part, by the anatomy and histology of the parts involved. These structures afford ideal "harbors of infection," in that they empty themselves from time to time, an optimum condition for the persistence of a virulent gonorrheal infection. This is particularly true of the cervical glands.

The constant effort to improve upon the old, unsatisfactory methods has brought forward, particularly within the last ten years, a number of promising procedures, either new in themselves or representing a new application of old principles. While it is not desired to present a review of this subject, it does seem worth while to mention, as outstanding examples, the negative pressure method of Moench, the injection method of Jacoby, the diathermy treatment and appliances of Corbus, the vaginal bag and hot water method of Elliott, the conization technic of Hyams and the actual cautery as advised and practiced by numerous individuals.

With the number of favored methods of treatment and the pessimistic trend of remarks heard in medical society discussions and, more often, in private conversation, there seems some justification for the analysis of the results of one of these methods in a clinic where distinct encouragement has been felt regarding the possibility of early cure in these cases.

The present analysis covers the work of the Gynecological Section, City Venereal Disease Clinic, in a city of about fifty thousand inhabitants. It covers a period of two and one-half years, from April 9, 1931, when it was decided to put a gynecologist in charge of this particular phase of the venereal disease work, to Oct. 9, 1933. During this period, approximately ten thousand visits were made by 574 patients. Needless to say, the usual difficulties attendant upon a City Venereal Disease Clinic along lines of continuity of treatment and follow-up were encountered. A number of patients with positive infections received no treatment, owing to prompt disappearance after the first visit. Many others disappeared before the completion of treatment. Again, the number of treated cases was reduced by the large number of "contacts" who proved persistently organism-free.

Of the 574 patients seen, 166 gave positive smears on the original examination; 123 gave suspicious smears (extracellular gram-negative diplococci); and 95 subsequently developed smears considered positive for Neisserian infection. Two hundred eighty-five gave negative smears at the original examination.

In spite of those lost sight of, a considerable number of patients in the positive group was carried to a satisfactory conclusion in the way of both treatment and follow-up. The total number giving positive smears at the first, or subsequent, examinations was 261. Of this number, 162 were carried to a definitely noninfectious stage. There were 17 patients described as refractory, of whom 10 were included in the list of cures, requiring from 8 to 11 treatments to attain this result, and 7 continue to show persistent, or occasional, positive smears.

The routine followed in this clinic has been to make a thorough pelvic examination at the first visit, taking smears and a blood Wassermann and employing the dark-field examination where indicated. In patients with syphilis, the treatment of that disease is conducted in another section of the clinic. It is of interest to note, in passing, that, of the 574 patients seen, 273 had syphilis. In patients with positive smears, local treatment is initiated at the second visit, unless inflammatory masses are found. In the latter case, foreign protein therapy is instituted and from 5 to 10 doses are administered before local treatment is initiated. At first, various proprietary preparations were employed, but the present medication consists of sterile, fat-free milk. In the local treatment of the cervix, the electric cautery is employed. On account of its simplicity and the wide choice of tips,

the Post instrument is used. In the parous cervix, which has not been extensively injured, the rod-shaped tip is placed in the canal, the current turned on and the appearance of a narrow, white rim of cooked tissue awaited. In nulliparous cervices, a smaller tip may be required. In extensively injured and eroded cervices, accompanying linear cauterization of the erosion will be required. Treatment is repeated at intervals of three weeks, smears being taken preceding each treatment, starting with the third. In the earlier cases, where the smears were taken before each treatment, there was an occasional persistent negative after a single treatment. However, this was so rare as to be negligible. After the first negative, the patient is required to return every two weeks for follow-up smears. This course serves a dual purpose. It gives an adequate follow-up and, as a public health measure, it permits supervision of the prostitute class for reinfection.

In the 162 cases carried to a persistent organism-free condition, the number of treatments required varied from an occasional single treatment to a small group of refractory cases requiring from 8 to 11 treatments. The average number of treatments for the entire group was 3.6. In addition to this larger number that is considered cured, there is a small group of 7 patients that shows either persistent, or occasional, positive cervical smears, in spite of thorough treatment. Among this latter group, one of three conditions is found: a persistent inflammatory mass, for which operation was refused; a considerably enlarged uterus, with persistent, thin discharge coming down into an apparently healthy cervix; or a very large, firm cervix. The second of these findings suggests the possibility of the occasional persistence of a gonococcal infection in the corpus uteri.

As might be expected in such a series, with the relatively severe type of cautery treatment and its frequent repetition in some cases, there was a considerable incidence of moderate stenosis of the cervix. This was considered sufficient to indicate dilatation in 18 cases. The dilatation was performed with the Hanks dilators and was gradually carried to the size sixteen instrument in three sittings, at weekly intervals.

As pregnancy is not a condition that is encouraged among the class of patients that constituted the great majority of this group, all that can be said in regard to the effect of cautery treatment in pregnancy is that, in a group of 500 cases, the cautery was employed, at first with reluctance but later without misgiving, and that the results were satisfactory. The feeling is that the cautery may be used in pregnancy for the treatment of gonorrheal cervicitis without undue fear of abortion.

In regard to the necessity for pelvic surgery in these cases, the records are incomplete, as the patients from this clinic find their ways

to both local hospitals, and there is considerable lack of coordination. It appears from the records that 42 of the 574 patients seen had undergone previous pelvic surgery and that 19 additional patients were so treated during the period under consideration. In several of this latter group, the pathology found was undoubtedly of long standing.

The following list summarizes the principal facts.

Number of patients seen		574
Number with positive cervical gonorrhea		261
Number receiving adequate treatment		169
Cures	162	
Failures	7	
Average number of treatments to cure		3.6

It is felt that any method of treating gonorrhea of the cervix that will render and keep organism-free 162 out of 169 patients, drawn principally from the prostitute class, is worthy of both consideration and confidence.

164 MARKET STREET

PYELONEPHRITIS OF PREGNANCY DUE TO *BACILLUS DYSENTERIAE*

REPORT OF A CASE WITH SURVEY OF LITURATURE AND COMMENT

G. R. CHEATHAM, M.D., ENDICOTT, N. Y.

(From the Department of Obstetrics, Endicott-Johnson Medical Service)

ONLY two cases of *B. dysenteriae* infection of the urinary tract are reported. The following case therefore has especial interest in its course, treatment, and outcome.

Mrs. A. C., aged twenty-five years, white, para iv. The family history was negative. At the age of fourteen she had an attack which was diagnosed appendicitis and was relieved by ice bags. There was no history of operations, accident, or serious illnesses. No history of gastrointestinal disorder: no loose, bloody, or mucous stools. She had had three normal, easy labors. The last menstrual period was May 15, 1932. She had not reported for antenatal care. On December 22, she slipped and fell in getting off a bus. She got up and walked home, when she developed moderately severe lower abdominal pains which she described as labor pains. Closer questioning revealed that there was constant pain radiating down the inner right thigh accompanied by burning and frequency. She was nauseated and vomited several times. There was some vaginal bleeding. I saw her for the first time at the office the next day. She still complained of pain, but the bleeding had stopped. She was well nourished, but acutely ill. Positive findings on examinations were: temperature 100° F., pulse 90, respirations 20. Uterus enlarged to size, shape, and consistency of seven months' gestation. There was rigidity and marked localized tenderness over McBurney's point. Vaginal examination showed no bleeding, no masses, but tenderness in right fornix. The patient was admitted to Ideal Hospital with the diagnosis of pregnancy complicated by right pyelitis or appendicitis. The

blood count on admission was 3,250,000 erythrocytes, 58 per cent hemoglobin: 9,000 leucocytes of which 81 per cent were polymorphonuclears, 18 per cent small lymphocytes, and 1 per cent eosinophils. The urine was cloudy, acid, specific gravity 1.012, and contained a definite trace of albumin, but no sugar; miscroscopically it showed no blood or casts, but was loaded with pus cells and contained a few epithelial cells. The surgeon called in consultation stated, "We know she has pyelitis from the urine, but with so much local tenderness and rigidity, I am afraid to let that appendix stay." The appendix was removed at once, December 24, McBurney's incision being used because of the impending labor. The appendix was not acutely inflamed but was bound down by adhesions from previous attacks. It was retrocecal. The pathologic report was, "A subacute or chronic appendix." The patient had some labor pains twenty-four hours after the operation. These subsided with morphine, but she began to vomit. She ran a "typhoid type" of temperature for the first week, and the vomiting increased from once a day, until by Jan. 2, 1933, about one-half of the total intake was being vomited. On the same day the urinary sediment showed many gram-negative bacilli, and the culture was reported as *Bacillus dysenteriae*. The wound was dressed Jan. 2, 1933; it was clean and healing though the patient complained of pain over the incision. The temperature was now more of a septic type, but the range of 101° F. to 102.4° F. was less than usually seen with pyelitis. On this day a No. 6 catheter was passed to the right kidney for drainage and left there for two days. The urethra was tight to a No. 20 cystoscope, the bladder inflamed, and the urine secreted under pressure. The temperature dropped to 101° F. for four days, but the vomiting and pain over the incision and the right kidney persisted. Urinary antiseptics given at this time were not retained, and no usual remedies for vomiting had any effect. Fluids were administered by vein, rectum, and under the skin. By Jan. 6, 1933, the temperature range was 99° F. to 105° F. and four days of this saw the patient worse. On Jan. 10, 1933, 4 c.c. of bacteriophage for *B. dysenteriae* (Anglo-French) were instilled into the right kidney, and 1 c.c. was given intramuscularly every three hours for two days, the total amount given being 20 c.c. The urine from the right kidney taken that day showed microscopically many pus cells, numerous clumps, a few granular casts and epithelial cells, and a very rare pus cast. Cultures from the right kidney were typical for *Bacillus dysenteriae* of the mannitol-fermenting group and gave the characteristic agglutination reaction with polyvalent dysentery serums. The patient's serum agglutinated *B. dysenteriae*, Flexner type, in dilutions of 1:640. The Widal reaction was negative.

The patient's condition remained about the same for the next week and then definitely improved. The temperature was lower, and vomiting decreased. On Jan. 28, 1933, thirty-six days after operation, she went into labor and delivered normally an eight months' live baby under gas oxygen anesthesia. A Beck binder had been used during labor because of the recent operation. She had a profuse postpartum hemorrhage which was controlled with pituitrin and gynergen. Her vomiting ceased with delivery. Two days later a blood transfusion of 350 c.c. was given, and from this time her recovery was surprisingly rapid. Her temperature was normal by Feb. 7, 1933, nine days postpartum, and only twice, at two-week intervals, did it show a twelve-hour exacerbation. At no time could *B. dysenteriae* be found in the stool or a history of dysentery be obtained. When Board of Health rules finally permitted her discharge under carrier restrictions, seventy-seven days postoperatively and forty-one days postpartum, the laboratory report was: "Organisms isolated from the stool are culturally *B. dysenteriae* but are not agglutinated by *B. dysenteriae* serums. Organisms isolated from the urine are culturally *B. dysenteriae* of the mannitol-fermenting group, and are agglutinated

by *B. dysenteriae* serums up to 1:640 dilution.'' Six weeks later three consecutive stool and urine cultures taken seven days apart were negative.

The only two cases of a similar condition that I could find in a review of standard textbooks and the literature were:

1. A. Foester in 1918 reported a cystopyelitis due to *B. dysenteriae* of the Flexner type six months after dysentery. The usual treatment for pyelitis plus autogenous vaccines failed to clear the condition. The patient was discharged improved after twelve weeks, but twelve months later he still had positive urinary cultures.

2. Calalb and Jonesco reported a pyelonephritis in a young woman commencing suddenly in the eighth month of pregnancy and proved bacteriologically to be caused by *B. dysenteriae*. Treatment by autogenous vaccines was effective, and there was no ill effect on the pregnancy. She gave birth to a normal child at term. No details are given as to previous illness or to stool cultures. Calalb and Jonesco reviewed the literature but were unable to find any cases. Hilgers isolated a pseudodysentery bacillus from two urines in 82 cases of urinary infections.

Autogenous vaccines were used in both these cases. These and antidysentery serum were considered in my case. The vaccines were discarded because we feared the let-down of the negative phase in a patient so ill. Serum was discarded because we did not see how it could aid when the patient's serum already had antibodies enough to give a strong definite agglutination against the organism. Mercurochrome intravenously was not given because of the danger of nephritis and what we consider its doubtful therapeutic value.

SUMMARY AND COMMENT

1. A rare case of pyelitis proved to be due to *B. dysenteriae* of the Flexner type is reported in detail.

2. Vomiting almost pernicious in type developed late in pregnancy after operation.

3. Vomiting prevented the use or appraisal of usual treatment of pyelitis.

4. The child was unaffected by the disease.

5. Delivery was followed by some improvement, but a small transfusion appeared to cause the real change.

6. Bacteriophage as used was of no value.

An unbiased review of this case brings out several points worthy of further discussion. It is not unknown to have pyelitis and appendicitis. The physical signs of appendicitis were found and appraised by a surgeon of vast experience and recognized ability, yet I now believe pyelitis the offender rather than the appendix and that the operation aggravated the vomiting.

We were dealing with what was to us at that time an entirely unknown condition and our therapy was naturally cautious. What usual therapy for pyelitis that was tried was largely defeated by vomiting. I have never encountered such persistent vomiting so late in pregnancy. Therapeutic induction of labor was seriously considered on several occasions. We were especially anxious to appraise the value of bacteriophage as a specific and gave no other treatment during its trial. Small transfusions were indicated and should have been used much earlier. Prenatal care would have prevented the development of the secondary anemia which in turn might have prevented the infection or at least modified its course.

SUBSEQUENT OBSERVATIONS

Patient was seen at the office Mar. 5, 1934, about four months pregnant with no complaints. Blood pressure 130:70 and voided specimen negative except for slight trace of albumin and few epithelial cells. No signs or symptoms of nephritis or

toxemia. She was told to return in two weeks, but on the day of return was admitted to the hospital complaining of abdominal pain.

The examination showed a very pale, anemic patient in constant but not severe pain with a fundus the size of a seven months' gestation. The fundus was rigid and tender throughout. There was no vaginal bleeding. Blood pressure 110:60. Catheterized specimen boiled solid with numerous granular and hyaline casts, occasional pus cells, and numerous red blood cells. The blood count was red cells, 2,750,000; white cells, 13,400 with 90 per cent polymorphonuclears and 10 per cent lymphocytes. A diagnosis of acute nephritis and premature separation of the placenta with concealed hemorrhage was made.

A donor was obtained for the transfusion. The uterus emptied from below by manual dilatation and extraction of a five months' fetus. The placenta showed red infarcts and an area of separation approximately over one-half its surface. There were very large clots behind the placenta. There was a fairly profuse postpartum hemorrhage. The patient was packed and given the transfusion. Two hours later she was bleeding through the packing. She was repacked and was in critical condition. A second transfusion was given. There was no more bleeding. The first day after delivery she was given another transfusion. Her temperature was 101° F. and stayed up so a series of ten Elliott treatments were given together with a fourth transfusion.

Twelve days after delivery the patient's general condition was good. There were no complaints. The temperature had been normal five days. Pelvic examination showed a third-degree retroversion. The urine report of a catheterized specimen was entirely negative except for a few pus cells. The red cell count was 3,490,000; white, 8,600 with 78 per cent polymorphonuclears; 16 per cent small lymphocytes; 3 per cent large mononuclears; 3 per cent eosinophils.

On the basis of her near disaster with the past two pregnancies, she was referred to surgery where a Baldy-Webster suspension, bilateral salpingectomy and ligature of varicose veins of both broad ligaments was done under spinal anesthesia. She had an uneventful convalescence and was discharged fourteen days following operation.

I wish to express my appreciation of the hearty cooperation and helpful suggestions of the consultant and laboratory staffs of Ideal Hospital.

REFERENCES

(1) *Foerster, A.:* München. med. Wchnschr. **65:** 205, 1918. (2) *Calalb, G., and Jonesco, V.:* Compt. rend. Soc. de Biol. **92:** 1460, 1925.

134 Washington Avenue

AN UNRUPTURED UTEROINTERSTITIAL PREGNANCY AT TERM*

EDWARD T. HULL, M.D., NEW YORK, N. Y.

(From the Gynecological and Obstetrical Service of the Lincoln Hospital)

FROM a survey of the literature of this subject it appears that most of the cases reported have been ruptured, usually at from two to seven months. Cases going on to term are exceedingly rare, and there are no instances where a live baby was obtained.

The following case is presented not only because of its rarity, but also because of the interesting efforts made at diagnosis before operation.

A. D., aged thirty, colored, para ii, previous history negative, was admitted to the Lincoln Hospital on Aug. 4, 1933, complaining of bleeding with passage of clots, of two weeks' duration. She had been amenorrheic for eight and one-half months, was gravid, and the estimated date of labor was Aug. 28, 1933. She had not felt the baby since the onset of bleeding. Physical and laboratory examinations were essentially negative. Pelvic examination showed a uterus which filled the abdomen. The external os was closed. Fetal outlines were felt, but no fetal heart could be heard. After four days in the hospital, her bleeding stopped, and as she showed no signs of being in labor she was discharged on Aug. 8, 1933. She was readmitted on August 29 for induction of labor and an attempt was made to rupture the membranes. This was unsuccessful. An x-ray picture was taken at this time to determine any abnormality. The report of the radiologist was, "X-ray shows the bones of a well-developed fetus in the abdomen. Position indeterminate." The fetal heart was never heard, nor did the patient state that she felt life. Because of the intrauterine manipulation as well as the presence of a dead fetus it was thought advisable to observe her, and the patient was discharged to the Out-Patient Department on September 12. She was admitted a third time on October 9, almost two months beyond the estimated date of labor, when I first saw her. The physical signs had not changed. On examination there was a tense abdomen, fetal parts were made out with difficulty, there were no fetal heart sounds. On vaginal examination, the cervix was only moderately softened, small, and did not feel like a normal, full-term cervix. Because of the long delay in the onset of labor and the findings on examination, an abdominal pregnancy was suspected, and in view of the dead fetus present which appeared certain, it was decided to make lipiodol studies. The x-ray plates taken after injection of the medium showed, besides the well-developed fetus, to the right in the abdomen extending up under the ribs, the outline of the uterine cavity below and to the left, just above the brim of the pelvis, with the left tube leading off at this same level. The right tube was not visualized. Upon this evidence a diagnosis of abdominal pregnancy was made. At operation a large sac was found apparently part of the uterus situated on the right side of the abdomen. This was incised and a dead fetus delivered. A typical supravaginal hysterectomy was then performed, leaving behind the left tube and the left ovary. Due to the firm attachment of the appendix to the inferior wall of the sac it was removed with the uterus. Postoperatively

*Read at a meeting of the New York Obstetrical Society, December 12, 1933.

the patient developed a pneumonia of the left lower lobe and also a stomatitis. Her recovery was otherwise uneventful and she left the hospital well.

The fetus weighed 9 pounds 2 ounces, was partially macerated, and had apparently been dead for some time. The uterus, amputated supravaginally in its entirety, corresponded to that of a term gravidity. Its upper part, extending on the right side, formed a cavity in which the fetus was present. This cavity was lined throughout by decidua and at its base a placenta was present. The entire sac occupied a position which would correspond in the nongravid state to the right uterine horn. Below the attachment of the placenta, the uterine cavity proper lined by typical endometrium was discernible. The wall of the uterus here was thick, hypertrophied, and resembled that of the nongravid state. No communication existed between the uterine cavity proper and the amniotic sac. With a fine probe it was possible to enter the true endometrial cavity through the stump of the left tube. On the right side the tube, markedly elongated, arose from the lateral wall

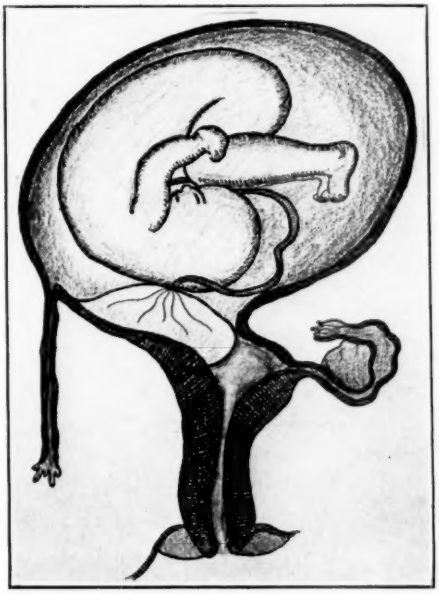


Fig. 1.—Partially schematic representation made from the specimen. The development of the pregnancy in the interstitial part of the right tube is demonstrated together with the approximate relationship of the structures involved.

of the sac. A probe passed through it showed it to be normal throughout its entire extent, and continuous with the amniotic cavity. The round ligament on this side was lower and considerably separated from the tubal attachment. A normal appendix was found attached by its tip to the inferior wall of the sac. Microscopic examination: Sections taken through the wall of the amniotic sac at different levels showed an uniform picture. The wall was markedly attenuated, but muscle tissue could be seen. In some sections chorionic elements had deeply invaded the myometrium. Decidua was present, but no uterine glands could be distinguished. In areas there were irregular infiltrations of small round cells. Sections taken through the wall of the endometrial cavity proper showed a normal endometrium and myometrium. Decidua was nowhere discernible.

Diagnosis.—Uterointerstitial pregnancy.

304 West Seventy-eighth Street

DISCUSSION

DR. GERARD L. MOENCH.—I would like to call attention to one sign or the absence of a sign which I have seen in three cases of interstitial pregnancy which I saw in about a period of a year and a half, and that is the absence of external bleeding with all the signs of ruptured ectopic gestation. It has worked out in my cases: after I had two I diagnosed the third one on the basis of these findings and the diagnosis was correct.

FULL-TERM TUBAL PREGNANCY REMOVED AT OPERATION TWO YEARS AFTER THE EXPECTED DATE OF CONFINEMENT*

HARRY W. FINK, M.D., CHICAGO, ILL.

THE patient was a multipara, thirty-one years old. Six years ago the left tube, ovary, as well as appendix were removed. Three years ago she became pregnant, went to term and after two attempts at induction of labor which failed she was allowed to go on, feeling perfectly well until three months ago, when she began to develop symptoms of toxemia, moderate temperature, nausea and vomiting. She also had pain in both lower quadrants, pressure on the rectum and bladder, backache, and loss of appetite. Her menses started one month after the second trial of labor and have continued regularly since. Upon examination there was tenderness in both lower quadrants and a palpable mass in the midline extended to three fingerbreadths below the umbilicus. This mass was hard, did not fluctuate and was fixed. Ten days ago she was operated upon. Wedged in the pelvis was a walled-off mass the size of a large fetal head. It was bound down by many adhesions especially to the sigmoid. The uterus was normal in size and rode high above the tumor. The right tube itself was not in evidence.

The specimen upon removal was an ovoid mass 14 cm. by 12 cm. It was partly covered by a fibrous sheet and in part by adipose tissue. Attached near the larger end was a pedicle 2 cm. long and 8 to 10 mm. in diameter composed of glistening fibrous tissue with a smooth central area of what appeared to be mucosa. No lumen could be found. On section the mass consisted of an outer sac with a wall 2 to 4 mm. thick and composed of glistening white tissue. Within the sac was a macerated, uncalcified male fetus. No fetal membranes were seen but an umbilical cord ran from the abdominal wall of the fetus to the inner surface of the sac where the wall was thickened to almost 1 cm. This area was composed of necrotic tissue suggestive of placenta. Sections of this area studied microscopically resembled tube wall and contained degenerated chorionic villi. Microscopic sections of the short pedicle show it to be definitely the isthmic portion of the tube. The histologic evidence favors the conclusion that this is an unruptured tubal pregnancy. The patient made an uneventful recovery.

---

*Presented to the Chicago Gynecological Society, February 16, 1934.

CEPHALOTHORACOPAGUS (DOUBLE MONSTER)*

GEORGE C. FINOLA, M.D., CHICAGO, ILL.

MRS. O. S., a thirty-six-year-old colored, gravida i, reported at St. Luke's Hospital on Jan. 31, 1934, because of a rapidly growing tumor in the lower abdomen just below the navel. This tumor which had been present for three weeks was a fibroid about the size of an orange. The patient knew that she was pregnant. Her last menstrual period occurred on Aug. 20, 1933, yet she thought that she had been feeling life for nearly eight weeks.

The physical examination was essentially negative. The uterus was the size of a seven and one-half months' pregnancy, and contained the unmistakable outlines of

Fig. 1.

a small fetus in the breech presentation with an excessive amount of amniotic fluid. Auscultation revealed only one set of fetal heart tones.

The diagnosis was intrauterine pregnancy, hydramnios, breech presentation, and uterine fibroid.

Two weeks later the patient returned with the following complaints: Extreme discomfort, inability to lie down or to sit up, urgency and frequency of urination, pain between the shoulder blades, and slight vaginal spotting. Blood pressure and urine again were normal.

The abdomen was enormously distended; the fundus reached the costal margin

*Presented at a meeting of the Chicago Gynecological Society, March 16, 1934.

31.5 cm. above the symphysis pubis. Because of the great tension of the uterine wall, the fetus could not be palpated. Fetal heart tones were faint. There was a moderate edema of the lower extremities.

X-ray examination was not made because the patient could not afford the additional expense.

In view of the patient's marked distress incident to the enormous hydramnios, and feeling relatively sure that she was carrying a monstrosity, it was decided to induce labor, Feb. 21, 1934, by giving castor oil and quinine, and later rupturing the membranes.

Six liters of amniotic fluid were collected. Labor pains were irregular and infrequent, at no time occurring more often than every six minutes.

The delivery was spontaneous and the mechanism was that of an O.R.A. Postpartum bleeding was not abnormal.

Fig. 1 shows the double monster or cephalothoracopagus, which weighed 3 pounds and 5 ounces. Both presented female genitalia and all extremities responded to stimulation. The fetus made several unsuccessful attempts to breathe and the heart continued to beat for three and one-half hours after birth.

Autopsy reveals two complete sets of apparently normal thoracic organs; those anteriorly placed belonging to the left incomplete twin and those in the posterior position belonging to the right incomplete twin. The anterior set of organs lacks 90° of the rotation necessary to achieve its normal position as does also the posterior set. Aside from the anomalous position of the organs in relation to the body cavities, there are other abnormalities as follows: A large patent arterial communication about 2 mm. in diameter extends between the arches of the 2 aortas. There are two sets of abdominal viscera except that there is but one esophagus, one stomach and a single small bowel down to a level of 10 cm. proximal to the ileocecal valve where the small bowel divides into two branches each of which continues as two distinct small and large bowels. A pancreas flanks each side of the duodenum and the biliary tracts from the 2 livers empty into the single small bowel at this level on opposite sides. The genitourinary systems are duplicated without anomalies.

TERMINAL ILEITIS RESEMBLING CLINICALLY AN OVARIAN CYST WITH TWISTED PEDICLE*

CAREY CULBERTSON, M.D., CHICAGO, ILL.

A MULTIPARA, aged forty-eight years, was admitted to the Medical Ward of Cook County Hospital complaining of a sudden attack of pain at night eight weeks prior, located in the right lower quadrant. A mass had formed which had not been observed previously. She had some nausea and vomiting after meals and dizziness. This had gone on for two weeks, then the sticking pain in the right lower quadrant appeared. She lost several pounds during the eight weeks and had night sweats.

The woman weighed over 200 pounds. A mass in the right lower quadrant rose as high as the crest of the ilium. It was firm and tender, and apparently not fixed to the abdominal wall. The lower pelvis was empty. We could not be sure that this mass originated in the pelvis. However, we had seen ovarian cysts that had become adherent and held out of the pelvis, so we considered this an ovarian cyst, and with this diagnosis she was operated upon.

---

*Presented at a meeting of the Chicago Gynecological Society, March 16, 1934.

The mass proved to be two kinks of ileum not more than 8 cm. above the cecum, adherent to the anterior abdominal wall on the right side and at about the level of the crest of the ilium. Wrapped around this adherent gut was the omentum which was infiltrated as well as adherent, and the two together formed a mass approximately 12 to 15 cm. in diameter. When this was freed, the ileum was found to be adherent at two points about four inches apart. Part of the omentum was resected and part left attached to the ileum in order to peritonize the raw area. The cecum and appendix were perfectly normal. This case, therefore, resolved itself into one of terminal ileitis. The patient made a good recovery.

CONGENITAL POSTNASAL POLYP IN THE NEWBORN CAUSING CYANOSIS

EDGAR HABECK, M.D., MILWAUKEE, WIS.

IT IS the purpose of this report to call attention to a rare cause of cyanosis, namely a pedunculated postnasal polyp.

When held upright or while nursing, the polyp descended from its postnasal position and projected into the pharynx. When the baby was lying flat the cyanosis was absent, but when held upright or its crib tilted in a Fowler position, we could at will cause a reappearance of the cyanosis.

Baby P, female, weight 7¼ pounds at birth, September 16, 1932, at the Deaconess Hospital, Milwaukee (normal delivery of a para i mother, aged 22, American born, after four hours of labor, ether anesthesia being employed in the latter part of the second stage), was cyanotic immediately after tying the umbilical cord. When the baby was laid across the mother's abdomen with its head downward, the cyanotic condition improved temporarily. The nurse in carrying the baby to the nursery, called my attention to the fact that the baby again became cyanotic, but upon placing it in a crib tilted in the Trendelenburg position, which is routinely employed for the first twenty-four hours, the cyanosis again disappeared. The heart sounds were normal, air entered both lungs, and the second day while taking the baby to breast the cyanosis again appeared and then the pedunculated polyp was discovered, but only while holding the baby in the upright position.

Dr. Jeffrey J. Brook, otolaryngologist, removed the polyp the second day, by the oral route, employing the ligation and snare method. There has not been a recurrence. The polyp was the size of an ordinary marble, pedunculated, and microscopically was a fibrolipoma. There was no family history of congenital malformations on either the maternal or paternal side.

405 EAST LINCOLN AVENUE

PROLAPSE OF THE FEMALE URETHRA

J. K. Ormond, M.D., F.A.C.S., Detroit, Mich.

(From the Division of Urology, Henry Ford Hospital)

THIS is an uncommon condition. A slight laxness of the meatus, or pouting of the meatal mucous membrane is frequent in elderly women, but actual prolapse is rarely seen. Our hospital case records now number over a hundred and ninety-five thousand (195,000) and that about to be reported is the only one of its kind in that number. The condition has been observed more frequently in some of the German Frauenkliniken, Säuferlin, for example, finding six instances in sixteen thousand admissions to one clinic in eleven years; and Würker, at another clinic, five cases in nine thousand admissions in nine years.

The discrepancy between these figures and ours may be partly explained by two considerations; first, that our hospital is a general hospital treating both sexes and all ages; and second, that our clientele embraces few from the indigent ranks of society, for there seems to be a definite relationship between this condition and faulty nutrition.

CASE REPORT

D. W., German, aged fifty-three years, had had a complete hysterectomy several years before, and had been under the care of the hospital intermittently for some years past because of mild chronic nephritis and obesity, and for various minor ailments.

Two days before admission she had noticed bleeding which she thought was of vaginal origin and which was profuse enough to necessitate the use of six napkins a day. Five days later she noticed a small tumor in the vulva. At no time was there any pain and there had been no urinary symptoms. She knew of no exciting cause for the bleeding or the appearance of the tumor.

The patient was a short stocky woman, slightly overweight. The general physical examination was practically negative.

A small, firm, dark red tumor, about the size of a cherry, was noted at the urethral meatus, which was bleeding slightly. In the apex of this tumor was a depression through which the catheter easily passed to the bladder, withdrawing clear urine. The tumor was not tender, and vaginal palpation showed that it did not extend up the urethra. Its surface was scaly, rather dry, but eroded in some places, from which blood oozed.

A diagnosis of strangulated and infarcted prolapse of the urethra was made and under nitrous oxide anesthesia it was excised with the radio knife. No sutures were used, but a soft rubber catheter was inserted and allowed to remain in place one day. She was discharged from the hospital the second day and nine days later had no discomfort or trouble beyond a slight oozing of blood. She disappeared from observation then for six months and it was later learned that a stricture had developed and required treatment.

Section showed that the vessels of the mucosa were markedly engorged and were thrombosed.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 12, 1933

The following papers and case reports were presented:

Temporary Exteriorization of the Uterus after Cesarean Section. Dr. H. R. Charlton.

Chorionepithelioma of the Uterus. Dr. T. C. Peightal. (See page 435.)

Unruptured Uterointerstitial Pregnancy at Term. Dr. E. T. Hull. (See page 452.)

Ventricular Cerebral Hemorrhage in the Newborn Infant. Dr. F. A. Hemsath. (See page 343.) (By invitation.)

The Treatment of Dysmenorrhea by Resection of the Presacral Sympathetic Nerves; Evaluation of End-Results. Dr. V. S. Counseller, and Winchell McK. Craig. (See page 161, August issue.) (By invitation.)

MEETING OF JANUARY 9, 1934

The following papers and case reports were presented:

Cornual Pregnancy of Eleven Months' Gestation. Dr. E. T. Hull.

A Parallel Study of Labor in the Young and Old Primipara. Dr. J. N. Nathanson.

Studies Relating to the Time of Human Ovulation. Dr. S. R. Kurzrok, I. J. S. Kirkman, and M. Creelman. (By invitation.) (See page 319.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 4, 1934

The following papers were presented:

Sympathoblastomas of the Vagina. Dr. Margaret C. Sturgis. (For original article see page 423.)

Avertin in Gynecology. Dr. R. B. Schutz. (For original article see page 439.)

Further Observations on the Effect of Female Sex Hormone Upon the Blood of Newborns. Dr. J. C. Hirst. (For original article see page 431.)

The Value of Postoperative Roentgen Irradiation in Carcinoma of the Ovary. Dr. J. B. Montgomery and Dr. J. T. Farrell. (For original article see page 365.)

MEETING OF FEBRUARY 1, 1934

The following paper was presented:

Experience with Radiation Therapy in Cancer of the Cervix. Dr. William P. Healy. (For original article see page 386.)

CHICAGO GYNECOLOGICAL SOCIETY

STATED MEETING, JANUARY 19, 1934

The following paper was presented:

Nonconvulsive Types of Toxemias in Late Pregnancy. Dr. Otto Henry Schwarz, of St. Louis (by invitation). (See page 334.)

MEETING OF FEBRUARY 16, 1934

The following papers were presented:

Treatment of the Uterine Hemorrhages Due to Benign Lesions With Radium and Roentgen Rays. Dr. Henry Schmitz. (See page 355.)

The Treatment of Fibroids. Dr. W. C. Danforth. (See page 409.)

Fibroids in Pregnancy. Dr. David S. Hillis.

Full-term Tubal Pregnancy Removed at Operation Two Years After the Expected Date of Confinement. Dr. Harry W. Fink. (See page 454.)

MEETING OF MARCH 16, 1934

The following paper and case reports were presented:

Embryology of the Female Genitourinary System and Its Relation to Obstetrics and Gynecology. Dr. Richard E. Scammon (by invitation).

Terminal Ileitis Resembling Clinically an Ovarian Cyst With Twisted Pedicle. Dr. Carey Culbertson. (See page 456.)

Cephalothoracopagus (Double Monster). Dr. George C. Finola. (See page 455.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D., ASSOCIATE EDITOR

Collective Review

TRENDS IN GYNECOLOGY AND OBSTETRICS DURING 1933

J. P. GREENHILL, M.D., CHICAGO, ILL.

(*Continued from August issue.*)

TOXEMIAS OF PREGNANCY

Before the American Gynecological Society, Adair presented an analysis of 262 cases of nonconvulsive toxemias of pregnancy. He divided these cases into two groups, one in which the symptoms develop abruptly in the later months of pregnancy, reach an acme during labor and subsequently tend to recede rapidly. In the second type, symptoms may be manifested early in pregnancy and become progressively worse. These patients also reach a climax usually in the later months of pregnancy. There is very slow retrogression of symptoms following delivery and the patients return to normal slowly if at all. Repeated pregnancies do serious damage, especially to the second group, and should be avoided. Adair's study emphasizes the importance not only of prenatal care but also of postnatal follow-up. Dieckmann (A.G.S.*) discussed comparative studies of the blood in the nonconvulsive toxemias of pregnancy and presented a large amount of valuable statistical information concerning the physicochemical analysis of the blood in these cases. Goodall (A.G.S.) took up the subject of nephritis and pregnancy and reviewed the histories of a few women who had nephritis during pregnancy, and who, instead of undergoing an aggravation of their kidney lesion, actually showed improvement. He agreed with Hofbauer that the toxemias of pregnancy are of endocrine origin and cited evidence in favor of this theory.

Hofbauer (U.C.) presented a masterly thesis in favor of his theory, first propounded in 1918, that overproduction of the posterior pituitary hormone is responsible for eclampsia and preeclampsia. On the basis of this theory he outlined his treatment of these toxemias. Fauvet (O) published a lengthy article bearing the title "Eclampsia, an Hypophyseal Disease" and he also presented an array of experimental and clinical evidence in support of Hofbauer's theory. Kleine (O) reviewed the various theories advanced to explain the onset of eclampsia and came to the conclusion that the placenta is responsible for the changes which lead up to eclampsia. He presented evidence to show that pregnancy is really a biologic battle. Theobald (O) stoutly maintained that toxemias of pregnancy are expressions of deficiency diseases as proved by the success he has had with calcium therapy. Rossenbeck (G.G.S.) believes that a disturbance in the carbohydrate metabolism is the chief difficulty in eclampsia.

Siegel and Wylie (O) found that convulsions are generally preceded by a fall in blood sugar. Wagner (A.M.A.) observed spastic lesions of the arterioles in

*For code see page 315, August issue.

70 per cent of patients with toxemia, but in about 60 per cent, these lesions disappear with the termination of pregnancy.

The prophylaxis of eclampsia was discussed by De Snoo (A.G.O.F.L. and G.G.S.) and he emphasized the early recognition of symptoms of toxemia and the prevention of convulsions. For this it is necessary to prescribe a diet without salt but with a normal amount of protein and fat and abundant water. Milk is forbidden because it contains 1.7 gr. of salt per liter. Waldstein (V.G.O.S.) prevents eclampsia in the puerperium by terminating labor artificially at the end of the second stage in women who have preeclampsia, by examining all women for symptoms of preeclampsia immediately after delivery and by instituting antieclamptic treatment as soon as any untoward symptoms are observed.

Solomons (A.A.O.G.A.S.) discussed albuminuria, eclampsism, eclampsia, hyperemesis gravidarum, and abruptio placentae and presented the methods of treatment of these conditions at the Rotunda Hospital and their results. The Rotunda conservative treatment of eclampsia has stood the test of time and to this Solomons has added the administration of glucose and venesection. Fauvet (G.G.S.) also favored conservative therapy in cases of eclampsia but praised pernocton as a valuable aid. Lazard (P.C.S.O.G.) reported good results in a series of 225 cases of eclampsia and 350 cases of preeclamptic toxemia treated by intravenous injections of magnesium sulphate which produces sedation and elimination. McIlroy (R.S.M.), Cosgrove (N.Y.S.M.S.), and Reinberger and Schreier (M.S.C.M.S.) made pleas for the conservative treatment of the toxemias of pregnancy with induction of labor should the patient fail to respond properly.

Arnold (C.C.M.S.) and also Bradford (S.D.M.S.) outlined their treatment of eclampsia by means of fluid limitation and cerebral dehydration. Lewis (T.S.M.A.) highly praised the intravenous administration of sodium amytal, and Hofbauer (U.C. and O), in addition to recommending the usual conservative measures, pointed out the advantages of alkalis and ultraviolet rays in the treatment of the toxemias of pregnancy. This therapy is based upon the fact that the principles of the posterior pituitary gland may be destroyed in a weakly alkaline medium or by ultraviolet rays. Hofbauer warned against the use of posterior pituitary preparations for the stimulation of uterine contractions during or after labor in women who have eclampsia or preeclampsia, because he has seen the outbreak of violent eclamptic seizures follow the injudicious use of pituitary preparations in hypertensive, edematous parturients. Basden (O) is in favor of cesarean section in cases of preeclamptic toxemia.

As Stander (O.S.P.) pointed out, the prognosis in chronic nephritis complicated by pregnancy is grave, the average maternal mortality occurring within ten years being approximately 40 per cent. He believes that the strain of pregnancy on kidney function greatly aggravates an underlying chronic nephritis and thereby materially shortens the life of the individual. On the other hand Theobald (O) presented statistics for England and Wales which tend to prove that pregnancy and childbirth have but relatively little causal association with chronic nephritis. He found that the differences in the mortality rates for chronic nephritis between married and single women during the childbearing period and for fifteen years afterward are so small as to be without marked statistical significance. Theobald refuted the increasingly expansive estimates of the frequency with which chronic nephritis is caused by the toxemias of pregnancy both because such views cause unnecessary anxiety and lead to an increase in the number of abortions and also because they tend to obscure the etiology of the toxemias and of Bright's disease. A. Evans (O) examined 76 women who had albuminuria during pregnancy from

four months to four years after they left the hospital and found definite chronic nephritis in 18 per cent of them and probable chronic nephritis in an additional 10 per cent.

Peckham (A.M.A.) studied the fetal mortality in cases of toxemia and found the following total rates: for low reserve kidney 9.46 per cent, for preeclampsia 17.06 per cent, for nephritis 25.49 per cent, for eclampsia 48 per cent and for toxemic vomiting 53.85 per cent. Peckham concluded that the outcome to the child renders dubious the wisdom of attempting to carry a patient in whom toxemia appears before the child is viable. With a child definitely viable and a toxemia appearing, its best chance seems to be in reasonably prompt induction of labor.

Strauss and McDonald (O) are of the opinion that polyneuritis of pregnancy is probably a dietary deficiency disorder similar to beriberi. Rational therapy should aim to supply the deficiency which may be some portion of the vitamin B complex. These authors suggest the prophylactic use of vitamin B in pernicious vomiting. Luikhart (C.A.O.G.) also considers avitaminosis (lack of vitamin B) as the likely etiologic factor in polyneuronitis, and he makes a plea for clinical and pathologic studies of the nervous system in hyperemesis gravidarum. The patient in the case reported by Luikhart responded to "washing out" with vitaminless glucose and saline, and there was a definite remission of symptoms after forced feeding with vitamin B complex for twelve hours. Van Del (O) reported three cases of polyneuritis; all of the patients improved on a high vitamin diet. Woltereck (H.O.S.) also reported a case. Plass and Mengert (A.M.A.) pointed out that gestational polyneuritis commonly follows or develops concurrently with hyperemesis. The cardinal symptoms are general weakness, sensory disturbances, tachycardia, diminution or absence of the tendon reflexes, and a psychosis of the Korsakoff type.

LABOR

Dyroff (G.G.S.) presented a long discussion on the onset of labor and propounded the theory that labor begins because the uterus reaches its maximum degree of hypertrophy beyond which further growth of the ovum produces distention of the uterine wall, increase in the uterine tonicity, and finally the reflex mechanism which is responsible for the emptying of the uterus. It is possible and likely that these reflex processes also act centripetally, and thereby stimulate an increased posterior pituitary secretion which is essential or at least useful for the maintenance of labor pains. Robson (E.O.S.) maintained that if it be accepted that the posterior pituitary hormone plays a rôle in parturition, it seems likely that estrin is to some extent at least, responsible for building up the reactivity of the uterine muscle which culminates in labor.

In a discussion on uterine action and its abnormalities before the British Congress of Obstetrics and Gynecology, Bourne pointed out that feeble contractions were the cause of many of the disasters of childbirth. He observed that nonengagement of the fetal head was often associated with inertia and that fear played a part in causing weak contractions. Bell, Datnow and Jeffcoate expressed the view that primary uterine inertia is due to lack of sensitization of the uterus by estrin and to insufficiency of the pressor substances in the maternal blood. The onset of labor and the occurrence of many cases of abortion seemed to be associated with an excess of estrin in the circulation. In Robson's presentation he mentioned that strips of human uterus removed during labor required a minimal dose of oxytocin to produce a contraction and that pieces from the lower uterine segment required ten times as much oxytocin as those from the upper segment. There was no effect in the early months of pregnancy, but there was an effect with small doses late in pregnancy. Taylor believed

incoordinate contractions during labor were due to the following causes: psychic, hormonic, mechanical, infection of the liquor amnii and oxytocics. Gilliatt took up the subject of contraction rings of the uterus during labor and advocated cesarean section as the treatment of choice for these cases. Rivett thought that differences in the thickness of the uterine wall were the cause of irregular uterine action, and Read emphasized the rôle of the mental aspect and sympathetic nervous system. Phillips agreed on the importance of fear, and Moir demonstrated waves of peristalsis in the uterus.

In a similar discussion on uterine inertia before the Royal Society of Medicine, Bell took up the matter of prophylaxis and treatment of uterine inertia in the first stage of labor. Marshall also dealt with the first stage and felt that inertia was a matter of derangement of the mechanics controlling uterine action. Maliphant blamed the stimulating mechanism of labor pains. Newton maintained that for efficient action of the uterine musculature there must be sufficient calcium in the blood, enough pressor substances and a properly developed neuromuscular mechanism. Wrigley discussed uterine inertia in the second stage and Turner dealt with this complication in the third stage.

Frankl (B.C.O.G.) spoke on the anatomy, physiology, and pathology of the isthmus uteri. He pointed out that the mucous membrane of the isthmus is always thinner, contains less glands than the corpus, and is much less able to respond to hormonal stimuli. A predecidual compacta does not develop in the isthmus at the premenstrual stage and correspondingly in pregnancy no true decidua compacta can be found. In pregnancy the isthmus takes part in the formation of the uterine cavity containing the ovum. Only exceptionally the isthmus develops a well-marked hyperplasia. Similarly as a rule, adenomyotic proliferation stops at the anatomical internal os.

An intensive study of comparative obstetrics led Rudolph and Ivy (C.G.S.) to conclude that the postural tone of the uterine musculature is the basic factor concerned in determining the presentation and position of the fetus. The attitude of the head in the presence of normal cephalopelvic relations is due to the intregration of three factors, namely, a harmoniously contracting uterus, the resistance to egress and the unequally balanced two-arm lever that exists between the vertebral column and the head. The authors made certain observations in human beings which indicate that the uterus may rotate the trunk and head of the fetus.

Mathieu (I.S.M.A.) induced labor in 96.8 per cent of 406 patients by means of castor oil and pituitary extract. This procedure failed to increase the maternal and fetal mortality, and morbidity. In fact Mathieu is confident that induction prevented maternal morbidity and saved several fetal lives. Voron and Brochier (A.G.O.F.L.) reported success in about 75 per cent of the cases where they employed castor oil, quinine, and pituitary extract near or at term. However, before eight and a half months of gestation, the results were unsatisfactory. Morton (O) employed castor oil, quinine, nasal pituitary extract, and artificial rupture of the membranes in 150 cases where the pregnancies had progressed beyond the period of viability, and he observed success in 98.7 per cent. The distinct shortening of the labors casts doubt on the statement that a dry labor is likely to be a long one. Bradford (T.S.M.A.) found artificial rupture of the membranes to be an efficient method of inducing labor in most cases. Kreis (O) explained the physiology and pathology of effacement of the cervix during pregnancy. He made a plea for artificial rupture of the membranes during labor, because this maneuver is not only excusable but is actually indicated due to the fact that the membranes freqently retard dilatation and effacement of the cervix. Van Rooy (O), on the other hand, feels that dry labor is an unfavorable complication and that premature interference endangers the life of the child.

In the opinion of Rudolph (A.A.O.G.A.S.), the anatomicophysiologic definition of a test of labor should be accepted rather than the clinical one, except for obstetric specialists. By the former term Rudolph means a test which begins only after complete dilatation of the cervix, rupture of the membranes, and a given number of hours of second stage labor. The clinical test of labor depends upon a variable number of hours of strong pains.

Browne (R.A.M.I.) presented a paper on the use of pituitary extract in labor which was discussed by a number of individuals. Solomons has gradually come to the conclusion that practically the only time to use this drug is after the third stage. Alden's paper (M.M.S.) on the same subject elicited lengthy discussions by Jackson and O'Brien. Lévy (S.O.G.S.) spoke on the use of thymophysin in obstetrics and said this drug marked a distinct advance in obstetrics. All five discussers of this paper emphasized the care with which the drug must be used. DerBrucke (O) showed that thymophysin produces a definite increase in blood pressure, and he emphasized the contraindications to its use. Hofbauer (O) presented evidence to show that the effects of thymophysin are due to the pituitary extract which it contains and that the indications, contraindications, time for employment, etc., which Temesvary laid down for thymophysin are the same as Hofbauer listed many years ago for pituitary extract.

MATERNAL MORTALITY

In his chairman's address, Hirst (A.M.A.) selected maternal mortality as one of the four major problems in gynecology. In his opinion the way to lower the maternal death rate is to have rigorous inspection of all hospitals receiving maternity cases. The state boards of licensure should supervise maternity hospitals and to a certain extent private practice in such hospitals as well. In the private house deaths, the chief fault is the lack of prenatal care. In discussing the same subject Bacon (A.A.O.G.A.S.) recommended to hospitals a number of general rules for the prevention of puerperal infections. Among them were the following: The obstetric staff of a hospital shall be responsible for the formulation of rules, for the management of the delivery rooms and for the care of the puerperas and for the carrying out of these rules. All cases requiring isolation shall be reported to the Health Department. Bacon like Hirst believes that the Health Department should institute a system of inspection of obstetric departments of hospitals. Skeel (A.A.O.G.A.S.) presented a simple and inexpensive plan for continuous study of obstetric mortalities as found in our large city hospitals. He emphasized that the measure of efficiency and safety of a maternity service is not the puerperal death rate of the hospital but the delivery death rate of its maternity service. These two rates in a maternity hospital may not be far different, but in a general hospital with active gynecologic and surgical services, the puerperal rate is often twice that of the delivery rate. Furthermore the method of calculation of death rates is wrong. The death rate should not be estimated only on the basis of live births alone but on total births, live ones as well as stillbirths.

The Committee on Public Health Relations of the New York Academy of Medicine presented a report on maternal mortality in New York City for 1930, 1931, and 1932. This report revealed the number of deaths due to anesthesia and operative deliveries, including cesarean sections; it compared hospital and home deliveries, and it reviewed the work done by the midwives of New York. The committee's conclusions and recommendations are well worth reading. Kosmak (N.Y.S.M.S.) discussed the maternal mortality rates in New York State and ventured the opinion that over half of the puerperal deaths, excluding abortions and nonpuerperal deaths, could be ascribed to faulty management, either

by the doctor or the hospital, over 17 per cent to the personal negligence of the patient or her family, and a very few to midwife participation, thus leaving about 30 per cent of the total in the nonpreventable class. Williamson (N.Y.O.S.) reviewed the records of 13,356 deliveries in an outdoor service and found that there were 48 maternal deaths in this series, an incidence of 3.6 per thousand. Ten of these deaths, however, were due to medical complications.

Rothert (O) presented an elaborate study based upon 7,380 deaths which occurred in fifteen states. The causes of death were as follows: accidents of pregnancy 10 per cent, puerperal hemorrhage 11 per cent, other accidents of labor 9 per cent, puerperal septicemia 40 per cent, puerperal phlegmasia alba dolens, embolus, and sudden death 5 per cent, and puerperal albuminuria and convulsions 26 per cent. Bolt (A.P.H.A.) found that among 151 puerperal deaths occurring during 1931 in Cleveland, 36 per cent were handled by specialists, 58 per cent by general practitioners, and 6 per cent by midwives. Gilliatt (K.C.H.M.S.) analyzed 2,000 maternal deaths and found that 626 could have been avoided since 226 were due to omission or inadequacy of antenatal care, 224 were caused by errors in judgment in the management of the case, 112 were due to negligence of the patient or her friends, and 64 were the result of lack of reasonable facilities.

Williams and Bishop (S.M.A.) showed what could be done toward lowering puerperal mortality in Tennessee by an intensive maternal hygiene program. Litzenberg (M.A.M.) demonstrated how the physicians of Minnesota are improving their obstetric practice and now have the lowest maternal mortality rate in the country (4.3 per 1,000 live births). Mendenhall (I.S.M.A.) emphasized that the way to decrease maternal deaths is to practice more conservative obstetrics, improve undergraduate education in obstetrics, extend postgraduate courses, educate the laity, add more maternities, supervise private and public hospitals, and familiarize the physician with obstetric literature and newer developments in the field of obstetrics.

DeLee and Siedentopf (O) presented a study of the incidence and causes of puerperal mortality and pointed out that whereas hospitalization of maternity cases is increasing everywhere, the puerperal death rate is not decreasing. They emphasize that meddlesome midwifery and puerperal infection seem to cause the greater part of the mortality. They believe that women are safer from infection at home or in a specialized maternity building than they are in the maternity wards of a general hospital. They, therefore, recommend architectural and administrative isolation of the clean maternity, until more is known about the nature of puerperal infection.

CARCINOMA OF THE UTERUS AND RADIATION THERAPY

At the Annual Congress of the American College of Surgeons, the title of one of the symposiums was "Cancer Is Curable." The results in the treatment of cervical cancer were reported by Keene, Taylor, Lynch and Bartlett, Burnam, Caldwell, Davis and Pomeroy. Other reports of late results in cervical cancer were published by Reiprich (G.G.S.), Göbel (G.G.S.), Fowler (F.A.C.C.), Dietel (G.R.S.), Saltzstein and Topcik (O), Ikeda and Ikeda (O) and Schilling (O).

The prophylaxis and early diagnosis of carcinoma of the cervix were discussed by Schmitz (S.M.A.) and also by Jones (O.S.M.S.). In a number of articles Hinselmann (G.G.S.) emphasized the histologic changes which take place in the cervix before carcinoma appears and also the early manifestations of carcinoma. He demonstrated the value of his colposcope as an aid in the prevention and early diagnosis of cervical cancer. Zweifel (B.S.O.G.) agreed with Hinselmann on the value of a colposcope and presented a new type of instrument. Schiller (O) reviewed in great detail the histologic changes of early carcinoma of the cervix

and again described the Lugol test for the detection of these cancers. Graves (C.C.A.C.S.) found Schiller's test an indispensable aid in the search for early cancer of the cervix. The test is specific for the absence of cancer.

Contrary to the opinion of many gynecologists, Philipp and Schäfer (O) do not believe that leucoplakia of the cervix is a forerunner of carcinoma. Among 49 cases of leucoplakia observed for as long as two and a half years, not a single cancer developed. However, these authors believe such patients should be carefully watched in spite of this. Hofbauer (O) presented evidence in favor of the hormonal origin of precancerous changes of the female generative tract. He (U.C.) found hyperplastic changes of the cervical epithelium in a number of pregnant uteri with well-defined ingrowths and hyperchromatism. Reasoning by analogy with similar phenomena in the gallbladder and breast, Hofbauer suggests that the production during pregnancy of solid tongues of proliferating epithelial cells in discrete places of the cervical mucosa may represent an important link in the chain of causative factors for the later development of malignancy. The practical lesson may be drawn that as an important element in cancer prophylaxis, proper care of the endocervix in the postnatal clinic requires careful inspection and immediate attention to any vascular or granular area. Te Linde (A.M.A.) described the histologic picture of cancerlike lesions of the cervix, attention to which will save many women from mutilating operations.

Crossen (A.G.S.) discussed in detail the prevention of cancer of the cervix, and he (I.S.M.S.) also elaborated on the surgeon's duty in cases of cervical cancer, not only from the point of view of prevention, but also from the angle of surgical and radiation treatment.

Jorstad and Auer (O) presented a histologic grading in carcinoma of the uterine cervix and discussed its relation to clinical grouping and prognosis. Maliphant (O) also presented a histologic classification and an analysis of the relation between cellular structure and prognosis after radium treatment. Philipp (O) maintained that before any operation for carcinoma is performed, a bacteriologic virulence test should be done and in endangered patients, radiation therapy should be employed before operation. If virulence tests are not performed, all cancer patients should be irradiated before operation. These beliefs are based upon the fact that the chief danger of the Wertheim operation lies in virulent streptococci, and the serious postoperative complications which result from these organisms may be prevented by radium therapy.

At the German Gynecological Congress, Miculicz-Radecki reviewed the subject of radical operation in elective cases of cervical carcinoma. In a series of 5,500 cases where operation was performed for operable cases and radiation therapy was used for the others, the incidence of cure was 24.5 per cent. Simple removal of the uterus will not suffice even if followed by intensive radiation because even in apparently localized cases, there may be metastases in the parametria. The results are the same for both abdominal and vaginal operations, but the operative mortality is 50 per cent less for the vaginal cases. Roentgen ray therapy should be used after every operation. Eymer (G.G.S.) reviewed the subject of radiation therapy in the treatment of cervical carcinoma. He compared a cure rate of 19.1 per cent for 5,806 operations with a cure rate of 19.7 per cent for 3,605 cases treated by radiation. Eymer emphasized that radiation therapy has a mortality of about 2.3 per cent. Kleine (G.G.S.) reported that whereas the incidence of cures of cancer in syphilitic and nonsyphilitic women was the same, the number of late radiation injuries was very high in the syphilitic group. He also pointed out that diabetic patients with cervical carcinoma react badly to radiation therapy. However, in cases of corpus carcinoma, radiation yields good results in diabetic women. The reason for this is not clear. Seventeen individuals participated in the discussion of this symposium.

Another symposium on the treatment of uterine carcinoma was presented before the German Roentgen Society. Schröder and Kirchhoff discussed the results with the Coutard x-ray treatment in 85 cases of cervical carcinoma and in 67 patients previously operated upon or treated with radium. Philipp presented the results obtained in Stoeckel's clinic. Among 2,090 cases of cervical cancer, the incidence of absolute cure was 26.9 per cent. For the 532 patients who were operated upon, the cure rate was 48 per cent and for the 1,555 irradiated patients it was 19.8 per cent. Wittenbeck used a concentrated method of applying x-rays and obtained a 24 per cent cure rate for cancers of the cervix and a 56 per cent cure rate for carcinomas of the corpus. Neff discussed the combined use of radium and x-rays and Reichenmüller described the changes in the blood during x-ray treatment.

Curtis (A.G.S.) advocated coincident surgical exposure through the vagina and radium therapy in the treatment of extensive cervical cancer, whereas Schumann (O.S.P.) favored direct intraabdominal radiation in advanced pelvic carcinoma.

Papers dealing with radiation therapy of cervical carcinoma were presented by Schmitz (R.S.N.A.), Heyman (O), Swanberg and Perley (A.C.P.T.), Leighton (A.A.O.G.A.S. and M.M.S.), Healy (N.Y.P.B.O.S.), Healy and Kelly (N.Y.A.M.), Kaplan (N.Y.A.M.) and King (E.O.S.). The technic of radiation therapy was described in detail by Schmitz (C.G.S.).

An interesting study was presented by Morton (A.R.S.) who showed that recurrence of carcinoma took place in about 50 per cent of Group I and II cases (operable cases) treated by irradiation. This is probably due to the persistence of live cancer cells in the cervix in a large proportion of cases. The author emphasized that the gross reaction of the cervix is not a reliable index of the adequacy of irradiation. He feels it is premature to discard surgery from consideration in the treatment of the early cases. Employing a combination of irradiation and surgery 67.8 per cent of operable patients seen in his clinic have been cured for more than five years. d'Erchia (O) advised the formation of an abscess by injecting turpentine before treatment with radium or by operation in cases of carcinoma.

Ward (Br.G.S.) presented a thorough and timely exposition of the complications of radium therapy in gynecology. In his series of 558 cases, 21.3 per cent had some postradiation morbidity, but most of them had minor discomforts. Not all of these complications can be avoided but they can be materially reduced in number if the action of radium on the tissues is understood, and meticulous care is taken in following the essential details of the preliminary treatment and technic of application. Colby (N.E.G.O.S.) discussed the urinary tract complications which occur in cases of uterine cancer, either from direct extension of the growth or as the result of radiation therapy. Dean (N.Y.O.S.) reviewed the etiology, pathology, symptomatology, diagnosis, prophylaxis, and treatment of urinary bladder injuries following irradiation of the uterus and reported a series of 47 cases which resulted after both radium and roentgen ray treatment for both benign and malignant uterine conditions. In every case the radiation therapy had been carried out by an experienced gynecologist. An average of two and one-half years elapsed between irradiation and the appearance of bladder symptoms. The onset was sudden, the suffering was intense in many cases and extensive destruction and even death followed.

Behney (A.G.S.) reviewed the reports of 166 necropsies on women who died with advanced carcinoma of the cervix and found that only 7 died from causes not dependent upon the cancer. In older women death was caused by secondary infection twice as frequently as in the younger ones. In the latter group exitus was more often the result of some mechanical cause such as obstruction of the ureters or hemorrhage. Involvement of the pelvic sympathetic nerves was

demonstrated and may have been a factor in the production of pain. In 132 autopsies on women dying of carcinoma of the cervix Warren (O) found a close relationship between the histologic grade of the tumor and the distribution of metastases. Eighty per cent of the metastases occurring after treatment appeared within one year. Ando (K.G.S.) reported bony metastases in two cases of uterine cancer, and Okabayashi and Houda cited other cases. Traube (S.E.G. G.S.) discussed the subject of vertebral metastases in the presence of cervical cancer and instances were reported by four discussers.

When cancer of the cervix recurs in the abdomen, Caffier (N.E.G.G.S.) advises operation if at all possible. Otherwise the patient is doomed. For small or superficial recurrences such as in the vagina or abdominal wall, one may choose between radium therapy and operation.

Hurdon (R.S.M.) reported the results with radium in the treatment of carcinoma of the body of the uterus. She mentioned that the combined results in 740 cases of nine leading clinics, showed a five-year survival rate of 32 per cent of all cases and 42 per cent of the operable cases. With modern technic the five-year survival rate of operable cases was from 70 to 80 per cent. Heyman (O) reported a five-year cure rate of 42.5 per cent for the 80 cases treated with radium by him but an unusually large proportion of these patients were inoperable. This author does not believe that adenocarcinoma of the body of the uterus is resistant to radium and he is of the opinion that the treatment of cancer of the uterine body should differ but little from the treatment of the same disease in the cervix. Dietel (G.R.S.) reported an absolute cure rate of 30.4 per cent for 92 patients with carcinoma of the corpus subjected to radiation therapy. Van Smith (O) reported a series of 181 cases of adenocarcinoma of the endometrium treated in various ways. Of the total, 51.3 per cent were alive five years after operation and 34.1 per cent were living ten years after operation. Of the 92 cases treated by complete hysterectomy 56.5 per cent survived five years, of the 39 who were subjected to supravaginal hysterectomy 53.8 per cent lived for at least five years and of the 21 who received radium 19 per cent were alive after five years. In cases of carcinoma of the corpus where because of complications a complete hysterectomy appears to endanger the life of a patient, Holtermann (O) advises a deep supravaginal hysterectomy.

A number of reports appeared dealing with surgical efforts to relieve the intractable pain associated with uterine carcinoma. Schück (O) advocated chordotomy, whereas Behney (O.S.P.), Wetherell (A.M.A.) and Greenhill and Schmitz (C.G.S.) claimed excellent results with pelvic sympathectomy.

OVARIAN TUMORS ASSOCIATED WITH SECONDARY SEX CHANGES

Under this title Novak (A.M.A.) reported a series of 26 granulosa cell ovarian tumors and one arrhenoblastoma together with a number of the tumors of the embryonic class, particularly disgerminoma (seminoma) and the so-called Brenner tumor (oophoroma folliculare). Novak emphasized particularly, (1) the feminizing tendency of the granulosa cell group, dependent on the production of folliculin by the constituent cells, and (2) the defeminizing and masculinizing tendencies of the arrhenoblastomas. The latter capacity is believed to be due to the origin of the tumors from certain undifferentiated cells in the region of the rete ovarii which is the female homologue of the testes. Most of the twenty-six cases of granulosa cell tumors which Novak reported were found by him during a restudy of the old material at the Johns Hopkins Hospital made because of the recent interest in these tumors. Novak's case of arrhenoblastoma is the fifth thus far reported in this country. The first was reported in 1921, the second in 1930, but the third and fourth were reported in 1933 by Spielman (O) and by

Taylor, Wolfermann and Kroek (O), respectively. The latter case is the twenty-seventh reported in the world literature. Mathias (S.E.G.O.G.S.) reported a case where an arrhenoblastoma was removed by operation and was followed by a pregnancy. This is the fifth case in the literature where gestation followed the removal of one of these masculinizing tumors.

Schulze (P.C.S.O.G.) reported seven cases of granulosa cell tumors and like Novak reviewed the histologic and clinical characteristics of these tumors. Wolfe and Kaminester (Br.G.S.) reported two cases, Brewer and Jones (O) three cases, Daily (O) two cases, Eiss one case and Klaften (V.O.G.S.) three cases of granulosa cell tumors.

Novak (A.G.S.) added three more cases of granulosa cell tumors which caused precocious puberty to the three already reported in the literature. As this author points out, while granulosa cell tumors are commonly classed as carcinomas, their degree of malignancy is usually slight, so that recurrence after removal is rather infrequent. In about 6 or 7 reported cases, all in adult women, the tumors have shown a high degree of malignancy. Kleine (B.O.G.S.) reported a case of granulosa cell tumor in a three-and-one-half-year-old child which he claims is the youngest on record to have such a tumor. This case was one of a series of twelve seen by Kleine. This author's experience leads him to the conclusion that granulosa cell tumors have a high degree of radiosensitivity.

The literature on Brenner tumors was reviewed by Freund (O) who says that up to the present time, 40 of these tumors have been reported. He added two of his own. It is the opinion of R. Meyer that these tumors arise from rests of coelomic epithelium. These completely undifferentiated cell rests possess the power to change under the influence of a general or local impetus such as hormones, change in nourishment or circulation. These tumors are benign. Plaut pointed out in his extensive report that Orthmann and not Brenner first described this type of tumor. For this reason Plaut suggested the name "fibroepithelioma mucinosum benignum." Other reports which appeared on Brenner tumors were those by Bettinger (S.E.G.O.G.S.), Derichsweiler (D.G.S.), Weinzierl (P.G.M.S.) and Abraham (G.S.B.). The case reported by the last author was associated with endometriosis. Those interested in Brenner tumors should read Robert Meyer's classic paper (Arch. f. Gynäk. **148:** 541, 1932).

185 NORTH WABASH AVENUE

REFERENCES

Abraham: Zentralbl. f. Gynäk. **57:** 1943, 1933. *Adair:* AM. J. OBST. & GYNEC. **26:** 530, 1933. *Akei:* Jap. J. Obst. & Gynec. **16:** 426, 1933. *Alden:* New England J. M. **209:** 1211, 1933. *Allen:* AM. J. OBST. & GYNEC. **25:** 705, 1933. *Ando:* Jap. J. Obst. & Gynec. **16:** 424, 1933. *Anschütz:* Zentralbl. f. Gynäk. **57:** 2021, 1933. *Anspach and Hoffman:* AM. J. OBST. & GYNEC. **26:** 147, 1933. *Arnold:* J. Med. S. New Jersey **30:** 22, 1933. *Aschheim:* Lancet **2:** 1370, 1933. *Aschheim and Hohlweg:* Deutsche med. Wchnschr. **59:** 12, 1933. *Bacon* AM. J. OBST. & GYNEC. **25:** 194, 1933. *Barrett:* Lancet **2:** 106, 1933. *Basden:* Brit. M. J. **1:** 58, 1933. *Béclère:* Gynéc. et Obst. **28:** 545, 1933. *Behney:* AM. J. OBST. & GYNEC. **26:** 608, 1933. *Behney:* Ibid. **25:** 687, 1933. *Bell:* Lancet **2:** 1345, 1933. *Bell, Datnow and Jeffcoate:* Ibid. **2:** 819, 1933, and J. Obst. & Gynec. Brit. Emp. **40:** 541, 1933. *Bemis:* AM. J. OBST. & GYNEC. **24:** 687, 1933. *Benthin:* Zentralbl. f. Gynäk. **57:** 1969, 1933. *Bettinger:* Ibid. **57:** 1377, 1933. *Bolt:* Am. J. Public Health **23:** 107, 1933. *Bourne:* Lancet **2:** 819, 1933. *Bourne and Bell:* J. Obst. & Gynec. Brit. Emp. **40:** 423, 1933. *Bradford:* Southern M. & S. **95:** 581, 1933. *Bradford:* Ibid. **95:** 9, 1933. *Brammer:* Zentralbl. f. Gynäk. **57:** 2808, 1933. *Brewer and Jones:* AM. J. OBST. & GYNEC. **25:** 505, 1933. *Brouha:* Gynéc. et Obst. **28:** 243, 1933. *Browne:* J. Obst. & Gynec. Brit. Emp. **40:** 390, 1933. *Burch and Burch:* AM. J. OBST. & GYNEC. **25:** 826, 1933. *Burnam:* Surg. Gynec. Obst. **56:** 427, 1933. *Caffier:* Ztschr. f. Geburtsh. u. Gynäk. **105:** 93, 1933. *Caldwell:* Surg. Gynec. Obst. **56:** 429, 1933. *Castallo:* New England J. M. **209:** 744, 1933. *Clauberg:* Zentralbl. f. Gynäk. **57:** 47, 1933. *Clauberg:* Ibid. **57:** 1895, 1933. *Clauberg:* Ibid. **57:** 1991, 1933. *Colby:* New England J. M. **209:** 231, 1933. *Collip, Selye, Anderson, and Thomson:* J. A. M. A. **101:** 1553, 1933. *Colloridi:* Ann. di ostet **55:** 187, 1933. Committee on Public Health Relations, J. A. M. A. **101:** 1826, 1933. *Cosgrove:* J. Med. New Jersey **30:** 6, 1933. *Cotte and Colson:* Lyon Chir. **30:** 314, 1933. Council of Pharmacy and Chemistry, J. A. M. A. **100:** 1331, 1933. *Crossen:* Illinois M. J. **64:** 123, 1933. *Crossen:* AM. J. OBST. & GYNEC. **26:** 686, 1933. *Curtis:* Surg. Gynec. Obst. **56:** 1052, 1933. *Curtis:* AM. J. OBST. & GYNEC. **26:** 569, 1933. *Daily:* AM. J. OBST. &

GYNEC. **26**: 733, 1933. *Davis:* Surg. Gynec. Obst. **56**: 430, 1933. *Dean:* AM. J. OBST. & GYNEC. **25**: 667, 1933. *DeLee and Siedentopf:* J. A. M. A. **100**: 6, 1933. *DerBrucke:* Am. J. Surg. **19**: 429, 1533. *d'Erchia:* Zentralbl. f. Gynäk. **57**: 435, 1933. *Derichweiler:* Zentralbl. f. Gynäk. **57**: 2259, 1933. *De Snoo:* Gynéc. et Obst. **28**: 527, 1933 and Arch. f. Gynäk. **156**: 211, 1933. *Dieckmann:* AM. J. OBST. & GYNEC. **26**: 543, 1933. *Dietel:* Strahlentherapie **46**: 201, 1933. *Doerfler:* Zentralbl. f. Gynäk. **57**: 2757, 1933. *Dyroff:* Arch. f. Gynäk. **156**: 164, 1933. *Eiss:* Am. J. Surg. **21**: 97, 1933. *Ekerfors:* Acta Obst. et Gynec. Scandinay. **13**: 13, 1933. *Evans:* J. A. M. A. **101**: 425, 1933. *Evans:* J. Obst. & Gynec. Brit Emp. **40**: 1024, 1933. *Eymer:* Arch. f. Gynäk. **156**: 268, 1933. *Fahmy:* J. Obst. & Gynec. Brit. Emp. **40**: 506, 1933. *Falkiner:* Irish J. M. Sc. **1**: January, 1933. *Fauvet:* Arch. f. Gynäk. **155**: 100, 1933. *Fauvet:* Ibid. **156**: 212, 1933. *Fluhmann:* Ann. Int. Med. **6**: 1212, 1933. *Fluhmann:* AM. J. OBST. & GYNEC. **26**: 642, 1933. *Fluhmann:* Endocrinology **17**: 550, 1933. *Forster:* J. Ind. State Med. Assn. **26**: 591, 1933. *Fowler:* Med. J. Australia **2**: 144, 1933. *Franken:* Arch. f. Gynäk. **156**: 66, 1933. *Frankl:* Lancet **2**: 820, 1933. *Freund:* Arch. f. Gynäk. **155**: 67, 1933. *Frigyesi:* Zentralbl. f. Gynäk. **57**: 1231, 1933. *Gabrielianz:* AM. J. OBST. & GYNEC. **25**: 499, 1933. *Gauss and Buschbeck:* Arch. f. Gynäk. **156**: 328, 1933. *Geiling:* J. A. M. A. **101**: 743, 1933. *Geist:* AM. J. OBST. & GYNEC. **26**: 588, 1933. *Gilliatt:* Lancet **2**: 1051, 1933. *Gilliatt:* Ibid. **2**: 820, 1933. *Göbel:* Arch. f. Gynäk. **56**: 288, 1933. *Gocke:* Zentralbl. f. Gynäk. **57**: 1808, 1933. *Goodall:* J. Obst. & Gynec. Brit. Emp. **40**: 640, 1933. *Goodall:* AM. J. OBST. & GYNEC. **26**: 556, 1933. *Graves:* Surg. Gynec. Obst. **56**: 317, 1933. *Greenhill:* South. M. J. **26**: 37, 1933. *Greenhill and Schmitz:* J. A. M. A. **101**: 26, 1933. *Haden and Singleton:* AM. J. OBST. & GYNEC. **26**: 330, 1933. *Hall:* Am. J. Surg. **21**: 272, 1933. *Hajek:* Zentralbl. f. Gynäk. **57**: 257, 1933. *Hartman:* AM. J. OBST. & GYNEC. **26**: 600, 1933. *Haultain:* Edinburgh M. J. **94**: July, 1933. *Haupt and Kraus:* Zentralbl. f. Gynäk. **57**: 129, 1933. *Healy:* AM. J. OBST. & GYNEC. **26**: 789, 1933. *Healy and Kelly:* Canad. M. A. J. **29**: 621, 1933. *Heard:* Canad. M. A. J. **29**: 164, 1933. *Heynemann:* Zentralbl. f. Gynäk. **57**: 2055, 1933. *Heyman:* Acta Radiol. **13**: 329, 1933. *Hinselmann:* Arch. f. Gynäk. **156**: 239, 1933. *Hinselmann:* Zentralbl. f. Gynäk. **57**: 1922, 1933. *Hinselmann:* Klin. Wchnschr. **12**: 1212, 1933. *Hinselmann:* Zentralbl. f. Gynäk. **57**: 2402, 1933. *Hirst:* AM. J. OBST. & GYNEC. **26**: 217, 1933. *Hirst:* J. A. M. A. **101**: 897, 1933. *Hirsch-Hoffman:* Arch. f. Gynäk. **156**: 42, 1933. *Hoevelmann:* Zentralbl. f. Gynäk. **57**: 2752, 1933. *Hofbauer:* AM. J. OBST. & GYNEC. **26**: 311, 1933 and Klin. Wchnschr. **12**: 369, 1933. *Hofbauer:* Zentralbl. f. Gynäk. **57**: 930, 1933. *Hofbauer:* Ibid. **57**: 2415, 1933. *Hofbauer:* AM. J. OBST. & GYNEC. **25**: 779, 1933. *Hofbauer:* Zentralbl. f. Gynäk. **57**: 872, 1933. *Holtermann:* Ibid. **57**: 1157, 1933. *Hubert:* Arch. f. Gynäk. **156**: 39, 1933. *Hübscher:* Zentralbl. f. Gynäk. **57**: 2844, 1933. *Huet:* Bull. et. mem. de la Soc. de Radiol Med. de France **21**: 561, 1933. *Hurdon:* J. Obst. & Gynec. Brit. Emp. **40**: 733, 1933. *Ikeda and Ikeda:* Radiol. Rundschau **19**: April, 1933 and Zentralbl. f. Gynäk. **57**: 1651, 1933. *Jameson:* AM. J. OBST. & GYNEC. **25**: 22, 1933. *Jayle:* Rev. franç de gynéc. et d'obst. **28**: 858, 1933. *Johnstone:* Brit. M. J. **2**: 557, 1933. *Jones:* Nortnwest Med. **32**: 53, 1933. *Jorstad and Auer:* Surg. Gynec. Obst. **57**: 583, 1933. *Kaplan:* AM. J. OBST. & GYNEC. **25**: 368, 1933. *Kaufman:* Zentralbl. f. Gynäk. **57**: 42, 1933. *Keene:* Surg. Gynec. Obst. **56**: 416, 1933. *Kelly:* Lancet **2**: 650, 1933. *Kennedy:* J. Obst. & Gynec. Brit. Emp. **40**: 792, 1933. *King:* AM. J. OBST. & GYNEC. **25**: 583, 1933. *King:* J. Obst. & Gynec. Brit. Emp. **40**: 383. 1933. *Kita and Okuni:* Jap. J. Obst. & Gynec. **16**: 421. 1933. *Klaften:* Zentralbl. f. Gynäk. **57**: 648, 1933. *Kleine:* Zentralbl. f. Gynäk. **57**: 2745, 1933. *Kleine:* Klin. Wchnschr. **12**: 1893, 1933. *Kleine:* Arch. f. Gynäk. **156**: 284, 1933. *Klingler and Burch:* AM. J. OBST. & GYNEC. **26**: 17, 1933. *Klingler, Burch and Cunningham:* Surg. Gynec. Obst. **56**: 137, 1933. *Klotz:* Arch. f. Gynäk. **156**: 45, 1933. *Kosakae, Ohga, and Okamoto:* Jap. J. Obst. & Gynec. **16**: 282, 1933. *Kosakae, Ohga, and Okamoto:* Ibid. **16**: 299, 1933. *Kosmak:* New York State J. Med. **33**: 1142, 1933. *Köster:* Zentralbl. f. Gynäk. **57**: 1524, 1933. *Kreis:* Gynéc. et obst. **27**: 97, 1933. *Küstner:* Zentralbl. f. Gynäk. **57**: 2870, 1933. *Lamarque:* Gynéc. et. obst. **28**: 291, 1933. *Lazard:* AM. J. OBST. & GYNEC. **26**: 647, 1933. *Leighton:* Am. J. Surg. **21**: 36, 1933. *Leighton:* Maine Med. J. **24**: 210, 1933. *Lévy:* Schweiz. med. Wchnschr. **63**: 1266, 1933. *Lewis:* AM. J. OBST. & GYNEC. **26**: 593, 1933. *Lewis:* J. Tenn. M. A. **26**: 392, 1933. *Litzenberg:* Minnesota Med. **16**: 287, 1933. *Litt:* AM. J. OBST. & GYNEC. **26**: 37, 1923. *Loeser:* Zentralbl. f. Gynäk. **57**: 2508, 1933. *Luikhart:* AM. J. OBST. & GYNEC. **25**: 810, 1933. *Lynch and Bartlett:* Surg. Gynec. Obst. **56**: 424, 1933. *Maliphant:* Lancet **2**: 1346, 1933. *Maliphant:* J. Obst. & Gynec. Brit. Emp. **40**: 444, 1923. *Marshall:* Lancet **2**: 1346, 1933. *Margraf:* Zentralbl. f. Gynäk. **57**: 1303, 1933. *Martindale:* Brit. M. J. **2**: 857, 1933. *Massabuau and Guibal:* Gynéc. et obst. **28**: 330, 1933. *Mathias:* Zentralbl. f. Gynäk. **57**: 449, 1933. *Mathieu:* Northwest. Med. **32**: 59, 1933. *Mavromati:* Rev. franç. de gynéc. et d'obst. **28**: 746, 1933. *Mavromati:* Ibid. **28**: 747, 1933. *Mayer:* Zentralbl. f. Gynäk. **57**: 2530, 1933. *Mellroy:* Lancet **2**: 1207, 1933. *Mendenhall:* J. Ind. M. A. **26**: 97, 1933. *Metz:* Zentralbl. f. Gynäk. **57**: 2638, 1933. *Mickuliez-Radecki:* Arch. f. Gynäk. **156**: 244, 1933. *Moir:* Lancet **2**: 820, 1933. *Moore:* AM. J. OBST. & GYNEC. **26**: 729, 1933. *Moriwaki:* Jap. J. Obst. & Gynec. **16**: 422, 1933. *Morton:* Am. J. Roentgenol. **29**: 487, 1933. *Morton:* AM. J. OBST. & GYNEC. **26**: 323, 1933. *Neff:* Zentralbl. f. Gynäk. **57**: 2441, 1933. *Neuweiler:* Schweiz. med. Wchnschr. **63**: 231, 1933. *Newton:* Lancet **2**: 1347, 1933. *Novak:* Brit. M. J. **2**: 553, 1933. *Novak:* J. A. M. A. **101**: 1057, 1933. *Novak:* AM. J. OBST. & GYNEC. **26**: 505, 1933. *Peckham:* J. A. M. A. **101**: 1608, 1933. *Peck and Goldberger:* AM. J. OBST. & GYNEC. **25**: 887, 1933. *Philipp and Schafer:* Zentralbl. f. Gynäk. **57**: 2407, 1933. *Philipp:* Ibid. **57**: 2417, 1933. *Philipp:* Ibid. **57**: 2439, 1933. *Philips:* Lancet **2**: 820, 1933. *Plass and Mengert:* J. A. M. A. **101**: 2020, 1933. *Pomeroy:* Surg. Gynec. Obst. **57**: 671, 1933. *Preissicker:* Zentralbl. f. Gynäk. **57**: 2637, 1933. *Reade:* Lancet **2**: 820, 1933. *Reichenmüller:* Zentralbl. f. Gynäk. **57**: 2442, 1933. *Reinberger and Schreier:* J. Tenn. M. A. **26**: 71, 1933. *Reiprich:* Arch. f. Gynäk. **156**: 283, 1933. *Rivett:* Brit. M. J. **2**: 778, 1933. *Rivett:* Lancet **2**: 820, 1933. *Robson:* J. Obst. & Gynec. Brit. Emp. **40**: 384, 1933. *Robson:* Lancet **2**: 820, 1933. *Roques:* Lancet **2**: 177, 1933. *Rossenbeck:* Arch. f. Gynäk. **156**: 206, 1933. *Rothert:* AM. J. OBST. & GYNEC. **26**: 279, 1933. *Rudolph and Ivy:* Ibid. **25**: 74, 1933. *Rudolph:* Ibid. **25**: 840, 1933. *Runge:* Arch. f. Gynäk. **156**: 27, 1933. *Sabaté:* Gynéc. et obst **28**: 548, 1933. *Sabel:* AM. J. OBST. & GYNEC. **26**: 417, 1933. *Saethre:* Klin. Wchnschr. **12**: 1727, 1933. *Saltzstein and Topcik:* Am. J.

Cancer **17**: 951, 1933. *Schiller:* Surg. Gynec. Obst. **56**: 210, 1933. *Schilling:* Zentralbl. f. Gynäk. **57**: 2422, 1933. *Schmid:* Arch. f. Gynäk. **156**: 56, 1933. *Schmitz:* South. M. J. **26**: 54, 1933. *Schmitz:* Radiology **21**: 311, 1933. *Schmitz:* Am. J. Obst. & Gynec. **25**: 10, 1933. *Schroeder:* Arch. f. Gynäk. **156**: 1, 1933. *Schroeder and Buschbeck:* Ibid. **156**: 40, 1933. *Schroeder, Kessler, and Tietze:* Zentralbl. f. Gynäk. **57**: 11, 1933. *Schröder and Kirchhoff:* Ibid. **57**: 2439, 1933. *Schulz:* Ibid. **57**: 2873, 1933. *Schulz:* Ibid. **57**: 1890, 1933. *Schulze:* Am. J. Obst. & Gynec. **26**: 627, 1933. *Schumann:* Ibid. **26**: 260, 1933. *Schück:* Zentralbl. f. Gynäk. **57**: 913, 1933. *Sevringhaus:* J. A. M. A. **101**: 2074, 1933. *Shaw:* Brit M. J. **2**: 907, 1933. *Siegel and Wylie:* Am. J. Obst. & Gynec. **26**: 29, 1933. *Skeel:* Ibid. **25**: 187, 1933. *Solomons:* Ibid. **25**: 172, 1933. *Spielman:* Ibid. **25**: 517, 1933. *Stalworth:* New Orleans M. & S. J. **86**: 298, 1933. *Stander:* Am. J. Obst. & Gynec. **26**: 183, 1933. *Stricker:* Zentralbl. f. Gynäk. **57**: 832, 1933. *Strauss and McDonald:* J. A. M. A. **100**: 1320, 1933. *Swanberg and Perley:* Arch Physiol. Therapy **14**: 604, 1933. *Szarka:* Arch. f. Gynäk. **156**: 325, 1933. *Taylor, Wolfermann, and Krock:* Surg. Gynec. Obst. **56**: 1040, 1933. *Taylor:* Surg. Gynec. Obst. **56**: 422, 1933. *Taylor:* Lancet **2**: 820, 1933. *Te Linde:* J. A. M. A. **101**: 1211, 1933. *Theilbaber:* Zentralbl. f. Gynäk. **57**: 833, 1933. *Theobald:* Brit. M. J. **2**: 376, 1933. *Theobald:* Lancet **2**: 626, 1933. *Tietze:* Arch. f. Gynäk. **156**: 35, 1933. *Traube:* Zentralbl. f. Gynäk. **57**: 2634, 1933. *Turner:* Lancet **2**: 1347, 1933. *Van Cauwenberghe:* Gynec. et Obst. **28**: 266, 1933. *Van Del:* Am. J. Obst. & Gynec. **25**: 564, 1933. *Van Del:* J. Missouri M. A. **30**: 407, 1933. *Van Rooy:* J. Obst. & Gynec. Brit. Emp. **40**: 850, 1933. *Van Smith:* New England J. M. **208**: 1049, 1933. *Van Smith and Rock:* Surg. Gynec. Obst. **57**: 100, 1933. *Vogt:* Zentralbl. f. Gynäk. **57**: 2875, 1933 and Ibid. **57**: 2638, 1933. *Voron and Brochier:* Gynéc et obst. **28**: 542, 1933. *Wagener:* J. A. M. A. **101**: 1380, 1933. *Waldstein:* Zentralbl. f. Gynäk. **57**: 497, 1933. *Ward:* Am. J. Obst. & Gynec. **25**: 1, 1933. *Warren:* Surg. Gynec. Obst. **56**: 742, 1933. *Wehefretz:* Arch. f. Gynäk. **156**: 40, 1933. *Weinzierl:* Med. Klin. **32**: 1078, 1933. *Werner and Collier:* J. A. M. A. **101**: 633, 1933. *Werner and Collier:* Ibid. **101**: 1466, 1933. *Wetherell:* Ibid. **101**: 1295, 1933. *Whitehouse:* Canad. M. A. J. **29**: 585, 1933. *Witherspoon:* New Orleans M. & S. J. **86**: 85, 1933. *Williams and Bishop:* South. M. J. **26**: 782, 1933. *Williamson:* Am. J. Obst. & Gynec. **26**: 911, 1933. *Wittenbeck:* Zentralbl. f. Gynäk. **57**: 2441, 1933. *Wolfe and Kaminester:* Am. J. Obst. & Gynec. **26**: 434, 1933. *Woltereck:* Zentralbl. f. Gynäk. **57**: 1952, 1933. *Wladika:* Ibid. **57**: 1974, 1933. *Wrigley:* Lancet **2**: 1347, 1933. *Yagi and Oga:* Jap. J. Obst. & Gynec. **16**: 427, 1933. *Yokota:* Ibid. **16**: 423, 1933. *Young and Others:* Edinburgh M. J. June, 1933. *Zondek:* Lancet **2**: 1256, 1933. *Zweifel:* München. med. Wchnschr. **80**: 1145, 1933.

Item

Quadrennial Prize of the International Foundation of Gynecology and Obstetrics

In order to perpetuate the intentions of the Committee having charge of the funds of the past International Congress of Gynecology and Obstetrics, the Administrative Council and the Consulting Committee of the Société Belge de Gynécologie et d'Obstétrique, the actual legal managers of the said funds, have decided to use the revenue of the foundation for a prize of ten thousand Belgian francs, to be awarded every four years.

The prize will be given to the author of the best paper in gynecology or obstetrics published during the four years preceding the time of the award.

The papers presented for this prize must be published in the official languages of the International Congress; namely, German, English, Spanish, French, and Italian, or translated into one of these languages.

Two copies of the paper must be sent to the Secretary of the Société Belge de Gynécologie et d'Obstétrique, twelve months before the fixed date for the award of the prize (Dr. Max Cheval, 16 Alphonse Hottat Street, Brussels, Belgium).

The Committee of Judges charged with the examination of the papers presented will be named by the Society from its active, corresponding and honorary members, national as well as foreign, and according to methods to be ultimately determined by the Society. The President of the Society will preside. The judges cannot take part in the contest.

The decision of the Committee of Judges will be made according to the majority of the votes. If no paper seems worthy of the prize, this will not be awarded and the amount will be added to the value of the next prize. The prize of the International Foundation of Gynecology and Obstetrics will be given, for the first time, in July, 1938, at the time of the monthly meeting of the Société Belge de Gynécologie et d'Obstétrique.